JOURNAL OF

The American Geriatrics Society

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FELLOWSHIP IN THE AMERICAN GERIATRICS SOCIETY AND SUBSCRIPTION TO THE JOURNAL

Fellowship in the American Geriatrics Society is open to all physicians who are members in good standing of their state or provincial medical societies and similar organizations in other countries. Fellowship dues, which include a subscription to the JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, are $15.00 per year. Application blanks may be secured from the Secretary, Dr. Malford W. Thewlis, 25 Mechanic Street, Wakefield, Rhode Island.

For purposes of simplicity, it has been decided that dues of any Fellows received up to September 30 will apply to the year in which they are received and that dues of new Fellows received after that date will apply to the subsequent year.

The JOURNAL OF THE AMERICAN GERIATRICS SOCIETY is the only official publication of the Society.

JOURNAL OF

The American Geriatrics Society

Official Journal of the American Geriatrics Society

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AMERICAN GERIATRICS SOCIETY

THE 1954 ANNUAL MEETING

The 11th Annual Meeting of the American Geriatrics Society will be held at the Fairmont Hotel in San Francisco, June 17 through 19.

Hotel reservations should be made through the San Francisco Convention and Visitors Bureau, 200 Civic Auditorium, San Francisco 2, California. Members should reserve accommodations immediately, stating times of arrival and departure, because the hotels expect to be filled to capacity.

The Annual Business Meeting will be held in the San Francisco Room of the Fairmont Hotel, Thursday morning, June 17, at 9 o'clock. All scientific sessions will be held in the Terrace Room. The Annual Dinner is scheduled for the Nob Hill Room on Friday evening, June 18, at 8 o'clock, preceded by cocktails in the Cirque Room Lounge at 7 o'clock.

The program will cover many aspects of geriatric medicine. There will be several panel discussions on subjects of current interest.

Dr. Laurance W. Kinsell, Highland Alameda County Hospital, 2701 Fourteenth Avenue, Oakland 6, California, is in charge of local arrangements for the meeting.

W. O. Thompson, M.D.
President

SCIENTIFIC PROGRAM

FAIRMONT HOTEL

THURSDAY, JUNE 17, 1954

8:00 A.M. Registration (*Terrace Room Foyer*)
9:00 A.M. Annual Business Meeting (*San Francisco Room*)
2:00 P.M. General Session (*Terrace Room*)

Norris J. Heckel, M.D., *Presiding*

1. Significance and Management of Genital Prolapse in the Aged
   Goodrich C. Schauffler, M.D., Portland, Ore.
2. Uterine Bleeding After the Menopause
   C. L. Buxton, M.D., New Haven, Conn.
3. The Use of Estrogens After the Menopause
   E. Kost Shelton, M.D., Los Angeles, Calif.
4. Cancer of the Breast—A Curable Disease
   H. Glenn Bell, M.D., San Francisco, Calif.

Edward Henderson, M.D., *Presiding*

5. The Psychology of Retirement
   Edward B. Allen, M.D. and Hollis E. Clow, M.D., White Plains, N. Y.
6. Criteria for the Feasibility of Rehabilitation in the Geriatric Patient
   Edward J. Lorenze, M.D., White Plains, N. Y.

Panel Discussion

7. RECENT DEVELOPMENTS IN CARDIOLOGY
   George C. Griffith, M.D., Los Angeles, Calif., Moderator
   Francis L. Chamberlain, M.D., San Francisco, Calif.
   William Paul Thompson, M.D., Los Angeles, Calif.

FRIDAY, JUNE 18, 1954

8:00 A.M. Registration (*Terrace Room Foyer*)
9:00 A.M. General Session (*Terrace Room*)

Edward B. Allen, M.D., *Presiding*

8. The Influence of Surgery in the Aged on Surgery in the Young
   Robert Elman, M.D., St. Louis, Mo.
9. The Diagnosis and Treatment of Diseases of the Bladder in the Aged
   Norris J. Heckel, M.D., Chicago, Ill.
10. The Fate of the Cholescystostomy Patient
    Daniel M. Hays, M.D. and Frank Glenn, M.D., New York, N. Y.
11. The Medical and Surgical Management of Acute Diverticulitis in Geriatric Patients
    Robert Priest, M.D., Brock E. Brush, M.D. and Louis Gregory, M.D., Detroit, Mich.

Malford W. Thewlis, M.D., *Presiding*

12. New Trends in the Treatment of Fractures of the Hip in the Aged
    Ralph Soto-Hall, M.D., San Francisco, Calif.
13. Management of Hip Fracture in the Geriatric Patient
    Charles V. Heck, M.D., Chicago, Ill.

Panel Discussion

14. METHODS OF DETERMINING OPERABILITY IN OLDER PATIENTS
    Warren H. Cole, M.D., Chicago, Ill., Moderator
    Differences in Physiology of the Young and Aged: Their Application to Operability—*Arthur J. Hunnicutt, M.D., Oakland, Calif.*
    Cardiac and Renal Reserve in the Aged as Related to Operability—*Charles T. Stone, M.D., Galveston, Texas*
    The Use of Laboratory Tests in Determining Operability—*Dr. Cole*

INTERMISSION FOR LUNCH

2:00 P.M. General Session (*Terrace Room*)

Elizabeth Mason-Hohl, M.D., *Presiding*

15. Overtreatment in the Aged
    Malford W. Thewlis, M.D., Wakefield, R. I.

16. Clinical Experience in Restoring Verbal Communication to 266 Laryngectomized Patients by Esophageal Speech
Lynwood Heaver, M.D., Willard White and Nona Goldstein, B.A., New York, N. Y.
17. The Influence of Endocrine Substances on the Metabolism in the Older Individual
William B. Kountz, M.D. and Teofil Kheim, M.D., St. Louis, Mo.
18. A Study of the Effects of Thyroid Medication on Pathology and Longevity in Aged Human Beings
Paul Starr, M.D., Los Angeles, Calif.

Warren H. Cole, M.D., *Presiding*

19. Hormones, Growth and Senescence
Laurance W. Kinsell, M.D., Oakland, Calif.

Panel Discussion

20. CHANGES IN STEROID EXCRETION WITH ADVANCING YEARS
Cornelius P. Rhoads, M.D., New York, N. Y., Moderator
Technical Advances in Steroid Measurement—*Thomas F. Gallagher, Ph.D., New York, N. Y.*
The Chromatograms of Urinary 17-Ketosteroids in Aged Persons Before and After the Administration of Stanolone and Testosterone —*Thomas H. McGavack, M.D., Sidney Pearson, Ph.D. and Helmut Haar, M.D., New York, N. Y.*
Adrenocortical Capacity and Metabolism of Hydrocortisone in Elderly Patients—*Frank Tyler, M.D., Salt Lake City, Utah*

ANNUAL DINNER, Friday, June 18, 1954

7:00 P.M. Cocktails—Cirque Room Lounge—Sponsored by the Schering Corporation
(Attendance limited to holders of dinner tickets)

8:00 P.M. Dinner (Dress optional)— Nob Hill Room
The dinner wine will be supplied by Wente Wineries, and the dessert wine by Cresta Blanca Wineries.

SATURDAY, JUNE 19, 1954

8:00 A.M. Registration (*Terrace Room Foyer*)
9:00 A.M. General Session (*Terrace Room*)

Hollis E. Clow, M.D., *Presiding*

21. Management of the Burned Elderly Patient
Sidney E. Ziffren, M.D., Iowa City, Iowa
22. Histologic Patterns of the Gastrointestinal Tract in Various Age Groups
Edward Henderson, M.D., Bloomfield, N. J.
23. A New Therapeutic Approach to the Management of Debilitating Diseases
Cortez F. Enloe, Jr., M.D., New York, N. Y.

Francis M. Pottenger, Jr., M.D., *Presiding*

Panel Discussion

24. THE RELATION OF INDUSTRY TO GERIATRICS
Carl M. Peterson, M.D., Chicago, Ill., Moderator

WHO SHOULD RETIRE?—*Charles E. Dutchess, M.D., New York, N. Y.*
THE IMPORTANCE OF GERIATRICS IN INDUSTRIAL MEDICINE—*Rutherford T. Johnstone, M.D., Los Angeles, Calif.*
THE STRESS DISORDERS—*William P. Shepard, M.D., New York, N. Y.*

25. TEMPORAL ARTERITIS
Bayard T. Horton, M.D. and Thomas B. Magath, M.D., Rochester, Minn.
26. PROGNOSIS AND TREATMENT OF OCULAR DEFECTS OF THE AGED
A. E. Maumenee, M.D., San Francisco, Calif.

TO BE READ BY TITLE

27. TUBE FEEDING WITH LIQUEFIED WHOLE FOOD IN ELDERLY PATIENTS
J. Barron, M.D. and L. S. Fallis, M.D., Detroit, Mich.
28. USE OF PSYCHOLOGIC TESTS IN DETERMINING PROGNOSIS AND TREATMENT IN GERIATRIC MENTAL ILLNESSES
D. V. Conwell, M.D., C. J. Kurth, M.D. and P. G. Murphy, Ph.D., Wichita, Kans.
29. MARRIAGE COUNSELLING IN GERIATRICS
A. K. Daniels, M.D., San Francisco, Calif.
30. STUDIES OF PLASMA HEPARIN LEVELS IN RELATION TO SEX, AGE, AND SERUM LIPIDS AND LIPOPROTEINS
H. Engelberg, M.D., Los Angeles, Calif.
31. BACTERIAL ALLERGY AS A CAUSE OF SO-CALLED INTRINSIC ASTHMA IN THE ELDERLY PATIENT
J. Forman, M.D. and H. Blatt, M.D., Columbus, Ohio
32. ARTERIAL DISEASE IN THE AGED
R. S. Gilfillan, M.D., San Francisco, Calif.
33. X-RAY FINDINGS IN GERIATRICS SURVEYS
G. J. Heppner, M.D., San Francisco, Calif.
34. STUDY OF THE PROBLEM OF PROSTHETIC FITTING AND TRAINING OF THE GERIATRIC PATIENT
M. K. Newman, M.D., Detroit, Mich.
35. SCREENING IN GERIATRICS
R. M. Perlman, M.D., San Francisco, Calif.
36. GERIATRIST-PHYSIATRIST TEAM IN GERIATRICS REHABILITATION
R. M. Perlman, M.D. and S. M. Dorinson, M.D., San Francisco, Calif.
37. BALLISTOCARDIOGRAPHY IN GERIATRICS
B. Schneider, M.D., Danville, Pa.
38. FURTHER CLINICAL STUDIES OF THE EFFECTS OF METRAZOL AND NICOTINAMIDE ON PSYCHIC AND MENTAL DISORDERS OF THE GERIATRIC PATIENT
Herman Seidel, M.D., Abraham A. Silver, M.D., Henry Nagel, M.D. and Jerome J. Blumberg, M.D., Baltimore, Md.

SCIENTIFIC SESSIONS ARE OPEN TO THE MEDICAL PROFESSION AND TO THOSE WHO ARE ESPECIALLY INTERESTED IN THE PROBLEMS OF AGING

PUBLICATION AGREEMENT WITH THE AMERICAN THERAPEUTIC SOCIETY

An agreement has been entered into whereby acceptable papers presented at the annual meeting of the American Therapeutic Society will be published in the *Journal of the American Geriatrics Society*. These papers will be subjected to the same careful editorial review as all others that are published in the Journal.

The manuscripts which appear in this Journal will later be included in the bound volume to be published by The Williams & Wilkins Company as the *Transactions of the American Therapeutic Society*. Dr. Francis M. Pottenger, Jr., Editor of the Transactions, has been made a member of the Editorial Board of this Journal.

The May issue of the *Journal of the American Geriatrics Society* has been designated an "American Therapeutic Society number" and only articles presented at the 1953 annual meeting of this society have been included. It was not possible to publish all the papers from this meeting in the May issue; additional articles will appear in later numbers.

An announcement of the 1954 Annual Meeting of the American Therapeutic Society appears elsewhere in this issue.

WILLARD O. THOMPSON, M.D.
Editor

EFFECTS OF SMOKING OF TOBACCO ON THE CARDIOVASCULAR SYSTEM OF NORMAL PERSONS AND PATIENTS WITH HYPERTENSION*

GRACE M. ROTH, Ph.D.

Section of Physiology, Mayo Clinic, Rochester, Minnesota

Although considerable evidence is available that the smoking of tobacco produces constriction of the blood vessels and changes in the electrocardiogram, some lack of agreement among investigators still remains. With more refined methods and better controls perhaps further agreement can be obtained.

All methods of measuring blood flow in man are indirect. However, irrespective of the methods, fundamental factors concerned with the status of the subjects, which bear directly on the measurement of blood flow in the extremities must be considered. These appeared to be 1) the environmental temperature; 2) the position of the subject, particularly of his extremities; 3) the taking of food; and 4) the basal metabolic rate.

METHODS

To control our smoking tests, data were obtained in a room kept at a constant temperature of 25.5°C. (78°F.) and a relative humidity of 40 per cent. The subjects fasted for fifteen hours before each test. During the test they wore lightweight short pajamas and were in a supine position on comfortable beds. At ten-minute intervals the temperatures of the plantar surfaces of both first and third toes and the volar sides of the distal phalanges of both first and third fingers were measured by copper constantin thermocouples designed by Sheard. Likewise, blood pressures and pulse rates were taken and the basal metabolic rate determined during the control period. When fairly constant readings of skin temperature, blood pressure and pulse rate were obtained, smoking was begun. Cigarettes of different brands bought on the open market were used. Two cigarettes were smoked in succession until two thirds of each had been smoked. Simultaneous determinations of blood pressure, pulse rate and skin temperature were made at intervals of one minute during the smoking period, which generally lasted twelve to sixteen minutes. Observations were continued for thirty minutes to an hour after smoking had ceased.

The subjects inhaled the tobacco smoke with the depth and the frequency to which they were accustomed. All unnecessary noise and other undesirable stimuli which might cause vasoconstriction were excluded.

RELIABILITY OF THE SMOKING TEST AND THE EFFECT OF HABITUAL SMOKING ON RESULTS OF THE TEST

Sixty-six standard smoking tests were carried out on 6 normal subjects (4 physicians and 2 women technicians) whose ages ranged from 21 to 44 years

* Read as part of a Symposium on Tobacco at the Fifty-fourth Annual Meeting of the American Therapeutic Society, New York, N. Y., May 29–31, 1953.

This paper will appear in the *Transactions of the American Therapeutic Society* for 1952–1953, which will be published by The Williams & Wilkins Company, Baltimore, Md

and whose basal metabolic rates ranged from −17 to +1 per cent, to determine whether the results of smoking tests made on the same individual from day to day are consistent and whether habitual smokers have such a tolerance to tobacco that they do not respond to smoking by vascular or physiologic change. All 6 subjects were habitual smokers and inhaled the smoke; this was also true of all the smokers used in the tests described subsequently. As controls, cigarettes of corn silk were smoked. The smoking of cigarettes of corn silk caused little or no change in skin temperature, blood pressure, pulse rate and electrocardiographic tracings.

During the smoking of two standard cigarettes, however, the skin temperature of the extremities of all of the subjects decreased an average of 2.5°C. (4.5°F.) with a range of 1° to 4.3°C. (7.7°F.) for the toes; for the fingers, the average decrease was 3.2°C. (5.8°F.) with a range from 1.2° to 6.5°C.

During smoking of the two standard cigarettes the average increase of blood pressure was 20 mm. of mercury systolic and 14 mm. diastolic. The pulse rate was increased an average of 36 beats per minute, ranging from 20 to 52 beats. The electrocardiographic changes consisted of increased heart rate, decreased amplitude of T waves and even inverted T waves in 1 instance.

After smoking ceased, the blood pressure, pulse rate and the electrocardiogram returned to normal within five to fifteen minutes. However, the peripheral vascular constriction indicated by the decrease of skin temperatures of the extremities persisted half an hour to an hour and in some cases much longer.

The skin temperature of the fingers and toes of subjects with variable basal metabolic rates generally decreased not more than an average of 2.5° to 3°C. during smoking.

These 66 standard smoking tests on 6 subjects showed that the response of the skin temperature of the same individual varied from day to day, according to the basal metabolic rate. Thus it was necessary to determine the basal metabolic rate and skin temperature for each study. Increases of the blood pressure and pulse rate during smoking varied little from day to day.

Habitual smokers did not show tolerance to the effects of smoking, as the skin temperature of the extremities decreased and the blood pressure and pulse rate increased during smoking of two standard cigarettes. The length of time the subject had been a smoker or the number of cigarettes smoked daily had no effect on the decrease of the temperature of the heaviest smoker.

EFFECT OF NICOTINE

To determine whether nicotine is the substance that causes the vascular effects, additional tests were made.

An isotonic solution of sodium chloride was given intravenously to each subject and then 2 mg. of nicotine was added to the solution. When the saline solution alone was given, the skin temperatures of the extremities dropped slightly; but when 2 mg. of nicotine was added to the solution without the subjects' knowledge, the skin temperature decreased rapidly.

When an isotonic solution of sodium chloride was given intravenously, the amplitude of the T waves in the electrocardiogram was slightly increased. When

2 mg. of nicotine was added to the solution and given through the same apparatus, the increase in heart rate and the decrease in amplitude of the T waves were even greater than those which occurred after the subject had smoked two standard cigarettes. These results seem to indicate that nicotine played a definite role in the vascular effects.

Commercial denicotinized cigarettes and cigarettes of low nicotine content are available and it was thought advisable to determine whether their use really protects the patient who needs to stop smoking.

From 30 smoking tests carried out with various commercial denicotinized cigarettes, it was found that the vascular effects were similar whether standard cigarettes or commercial denicotinized cigarettes were smoked.

Since commercial denicotinized cigarettes and standard cigarettes produced the same vascular effects but none could be produced by really nicotine-free cigarettes, it seemed desirable to learn how much the content of nicotine in a cigarette should be decreased to banish vascular effects.

One hundred ninety-two standard smoking tests were made on 29 normal subjects, whose ages ranged from 20 to 36 years. Six different batches of cigarettes were used. The main stream of the smoke from one cigarette of each batch contained, respectively, an average of 0.23, 0.55, 1.28, 1.83, 2.47 and 3 mg. of nicotine. When the cigarettes were smoked, neither the subject nor the technician who was carrying out the test knew which cigarette was being used. As a control, corn-silk cigarettes were smoked. Basal metabolic rates were determined almost every time a smoking test was made.

During smoking of the cigarette with the lowest concentration of nicotine (0.23 mg.) in the stream of smoke, the decrease of the skin temperature of the toes was similar to that when corn-silk cigarettes were smoked, but the skin temperature of the fingers was somewhat greater than when corn-silk cigarettes were used. As the concentration of nicotine in the main stream of the cigarettes was increased, the skin temperature of both the fingers and toes decreased until the effects were the same as with the standard cigarettes.

The lower the concentrations of nicotine in the smoke, the less the increase of blood pressure and pulse rate from the basal level. As the concentration of nicotine increased, both blood pressure and pulse rate increased; the increase was sharp when the concentration of nicotine was raised from 0.55 to 1.28 mg.

From the studies described, it seems evident that nicotine plays the most important role in production of the vascular changes which accompany smoking. Likewise, these observations explain why the same vascular effects were obtained during the smoking of standard cigarettes and denicotinized cigarettes. Whether the tobacco is denicotinized or whether the tobacco originally is low in nicotine, apparently the content of nicotine in a cigarette must be decreased more than 60 per cent before the vascular effects of smoking fail to appear or are only slight.

ALCOHOL AND SMOKING

Smoking, then, constricts the blood vessels of the extremities, whereas alcohol dilates the blood vessels. Therefore, can the oral administration of 95 per cent

ethyl alcohol prevent the constriction of the peripheral blood vessels known to be produced by the smoking of tobacco?

Observations were made on 65 normal individuals—6 women and 59 men; ages ranged from 19 to 59 years, and basal metabolic rates ranged from −21 to +5 per cent. Many of the subjects were physicians.

Control smoking tests were made on one day and the effect of smoking after the taking of alcohol was investigated on the next. The effect of smoking for the control test persisted too long to make it feasible to carry out both investigations on the same day.

Eighty-seven smoking tests were made after the taking of alcohol. For this test, each subject took 30 cc. of 95 per cent ethyl alcohol in 250 cc. of fruit juice. This amount is equivalent to 2 fluid ounces (60 cc.) of whiskey. When either is given on a fasting stomach, the amount is sufficient to produce definite dilatation of the peripheral blood vessels. The standard smoking test was carried out, as an increase of the skin temperature of the toes and fingers indicated vasodilatation.

The response to smoking after the taking of alcohol, made by 72 per cent of the subjects, was a rise in the blood pressure and pulse rate which was definite but only slightly smaller than the rises which occurred during smoking alone. The skin temperature of the fingers and toes decreased below the basal level that had been determined before alcohol had been taken. Since the height of vasodilatation which follows ingestion of alcohol does not occur until sufficient alcohol has been absorbed, it may not be reached until fifty to sixty minutes after ingestion of alcohol. The height of vasodilatation once reached, however, persists for sixty to ninety minutes.

Smoking tests, from thirty to ninety minutes after the ingestion of alcohol, demonstrated that the alcohol did not prevent vasoconstriction from smoking.

This study then does not substantiate the common belief that drinking a cocktail will necessarily nullify the effect of smoking.

HYPERTENSION AND SMOKING

Next to be considered is the effect of smoking in patients with hypertension.

Smoking tests with standard cigarettes were carried out on 26 patients who had a labile blood pressure. During the smoking the systolic blood pressure increased an average of 38 mm. of Hg, with a range from 24 to 57, and the diastolic blood pressure increased an average of 30 mm., with a range from 18 to 35. The average basal blood pressure of these 26 patients was 128 mm. systolic and 93 diastolic.

Similar tests carried out on 16 patients with hypertension disclosed an average increase of 38 mm. in the systolic blood pressure, with a range from 34 to 52, and an average increase of 23 mm. in the diastolic blood pressure, with a range of 24 to 34 mm. The average basal blood pressure of these 16 patients was 170 mm. systolic and 117 diastolic.

Since in the hypertensive patient the rise of the blood pressure is greater than in the normal individual, it would be wise to advise the hypertensive patient to cease smoking.

PHARMACOLOGY OF TOBACCO*

CHARACTERISTICS OF CIGARETTE SMOKE

HARVEY B. HAAG, M.D.†

Medical College of Virginia, Richmond, Virginia

This discussion will deal with tobacco smoke. Therefore, preliminary to discussing its pharmacology, it seems desirable first to consider its composition. Because of the relatively greater use of tobacco in the form of cigarettes in comparison with its use in pipe and cigar smoking, only the composition of cigarette smoke will be presented. The data were obtained on "regular" sized cigarettes, which weigh approximately 1 gram and contain about 2 per cent nicotine calculated on the basis of dry weight.

Cigarette smoke (an aerosol) may be divided into a) "side-stream smoke," *i.e.*, that which goes off into the atmosphere from the burning tip, and b) "main-stream smoke," *i.e.*, that which is puffed by the smoker.

The composition of the side-stream smoke will not be considered, since aside from having an irritating alkaline character, it ordinarily has no physiologic import.

Because the quantitative composition of main-stream smoke varies considerably, depending upon the conditions under which it is produced, these conditions must be defined in connection with the analytical values. The values to be cited were obtained by use of a smoking machine in which the puff was drawn as a result of suction created by a falling column of water of predetermined volume. When the main-stream smoke of an average regular sized cigarette is collected by thus drawing 35-cc. puffs of two seconds' duration, once a minute until two thirds of the cigarette is consumed (conditions which approximate average smoking), chemical analysis of the smoke collected (350 cc.) gives the following average figures:

The nicotine in this main-stream smoke represents approximately 22 per cent of that originally present in the burned portion of the cigarette. Of the remainder, about 35 per cent volatilizes into the side-stream smoke, a similar amount is destroyed at the burning tip, and about 6 per cent condenses and collects in the non-burning butt.

The temperature of the main-stream smoke at the time of its entry into the mouth does not rise above body temperature until the last fourth or so of the cigarette is smoked, at which point the temperature may quickly rise to 112°F. Smoke temperatures above 135°F. are definitely uncomfortable to the tongue and mouth. The burning tip has a temperature of around 1425°F.

* Read as part of a Symposium on Tobacco at the Fifty-fourth Annual Meeting of the American Therapeutic Society, New York, N. Y., May 29-31, 1953.

This paper will appear in the *Transactions of the American Therapeutic Society* for 1952-1953, which will be published by The Williams & Wilkins Company, Baltimore, Md.

† Professor of Pharmacology.

II. PHARMACOLOGIC ACTIONS OF CIGARETTE SMOKE AND CERTAIN OF ITS CONSTITUENTS

A. *Local irritative effects*

The nature of this presentation allows for but a brief statement with reference to the difficult problem of measuring the irritating effects of cigarette smoke and its constituents. Experiments have demonstrated that the response may be of an objective or subjective character. The experimental data on the objective response have been obtained primarily through use of the rabbit-eye technic, in which the degree of irritation in the form of edema is determined gravimetrically. That this objective criterion alone does not give a complete picture of the total irritating potency of cigarette smoke is shown by the finding that the smoke of two cigarettes of different composition may have identical edema-provoking properties and yet differ markedly when tested subjectively on man. This discrepancy is largely due to differences in the smoke bases, notably nicotine; nicotine alkaloid can produce pronounced phenomena of acute subjective irritation without provoking any signs of objective irritation. Fortunately the salts of nicotine are relatively nonirritating as compared with the free base. Hence, in a well blended cigarette the amount of free nicotine alkaloid in the smoke is minimized through proper use of a mixture of "acid" and "alkaline" types of tobacco. There are no adequate means available for determining directly in man the overall irritation due to cigarette smoke. That subjective evidence of irritation may result from ordinary cigarette smoking is unquestionably true; that objective phenomena of irritation ordinarily result seems far from established.

The so-called "tars" from cigarette smoke, when freed of water-soluble substances, are not acutely irritating objectively or subjectively when tested on the rabbit eye, the only response being that observed from any inert foreign body.

B. *Systemic effects*

Most observers are of the opinion that the systemic effects resulting from the smoking of cigarettes are due to nicotine present in, and absorbed from the smoke.

1. *Absorption of nicotine:* Experience gained from clinical observations and animal experimentation demonstrates that nicotine is much more quickly absorbed from skin and mucous membranes as the free alkaloid, than when it is in the form of one of its salts such as the sulfate. This is of especial practical importance in connection with industrial and agricultural application of nicotine and its preparations. In the case of cigarette smoking by man, it has been shown that, on inhalation of the smoke, about 90 per cent of the nicotine contained in it is absorbed. Hence if the amount of nicotine in the total main-stream smoke of a cigarette is 3 mg., approximately 2.5 mg. can be expected to be absorbed. In the case of noninhaling smokers, the average figure is much lower. In these smokers, although there are marked individual variations, approximately only 10 per cent of the nicotine is absorbed. This ordinarily would amount to about 0.3 mg. In any given smoker, therefore, any degree of absorption between these limits may be attained, depending upon the individual's smoking habits.

2. *Fate of absorbed nicotine:* In the case of man it has been demonstrated that about 10 per cent of the nicotine absorbed is eliminated as such, primarily by way of the urine, although traces may be found in other secretions and excretions.

In spite of the large amount of research on the subject, the fate of the remaining 90 per cent of the absorbed nicotine is not yet established. It is known that this fraction is not converted into nicotinic acid and related compounds. There is good evidence, on the basis of animal experimentation, that the pyrollidine ring of the nicotine molecule splits between the nitrogen and the 5 position to form a pyridine amino acid, but the further fate of this compound has not been reported.

Although the exact products of nicotine detoxication are not known, much has been learned concerning the possible sites of its destruction, on the basis of both *in vivo* and *in vitro* experiments. Results derived from the latter type of study show that human liver, lung, kidney and brain slices are quite active in their ability to alter the nicotine molecule; liver tissue has been found the most active. That the liver is important *in vivo* is attested by the finding that in animals with experimentally induced hepatic damage, nicotine is appreciably more toxic than when administered to normal animals.

3. *Rate of nicotine elimination (detoxication and excretion)*: Using randomly labeled C^{14} nicotine, it has been shown in rats and dogs that virtually all of the C^{14} contained in a single administered dose is eliminated in the urine within twenty-four hours, either as unchanged nicotine or its metabolites. Incidentally this labeled nicotine was extracted from tobacco plants grown in an atmosphere containing $C^{14}O_2$. Although the rate of elimination by man is not definitely known, it must be fairly rapid, since the smoker of two packages of cigarettes a day may absorb an amount of nicotine regarded as potentially lethal (60 mg.) when taken at one time. One study involving the determination of nicotine or nicotine-like substances in the blood has shown that, during the course of smoking 20 cigarettes in seven hours, 80 to 95 per cent of the nicotine estimated to have been absorbed was eliminated during the period of smoking. From this observation and from the animal experiments referred to, it appears that neither nicotine nor its products of metabolism are ordinarily retained in the body to any significant extent.

4. *Fundamental physiologic nature of the systemic effects of nicotine:* Nicotine acts like acetylcholine upon autonomic (sympathetic and parasympathetic) ganglia and skeletal muscle, as well as acting upon the central nervous system. The action at all three sites is one of stimulation followed by depression. With the amount of nicotine encountered in smoking, the stimulating effect is the one ordinarily noted.

The eventual results brought about by this stimulatory effect on autonomic ganglia will usually depend on whether sympathetic or parasympathetic ganglia are primarily involved. For instance, the usual effect of smoking on the heart rate seems to be a reflection of pure stimulation of sympathetic ganglia; occasionally, however, bradycardia occurs as the result of predominating parasympathetic ganglionic stimulation. It is this dual action which makes for the unpredictability of the ultimate response to nicotine of structures both sympathetically and parasympathetically innervated. It is possible that no de-

monstrable effect would occur in a given tissue if the intensity of action on sympathetic ganglia were to balance that on parasympathetic ganglia.

5. *General effects on the cardiovascular system:* The usual effect of smoking on the cardiovascular system is an increase in heart rate, an increase in blood pressure and a decrease in skin temperature of the extremities (resulting from peripheral vasoconstriction). These effects are due to the stimulation of sympathetic ganglia plus some increase in the secretion of epinephrine due to excitation of the adrenal glands. Ordinarily, these cardiovascular effects persist for about thirty minutes.

6. *General effects on the gastro-intestinal tract:* The general response of the gastro-intestinal tract to cigarette smoking is by no means as well defined as in the case of the cardiovascular system. Depending upon which of the autonomic ganglionic systems is more stimulated, there might result an increase, a decrease or, if one stimulation balances with the other, no effect. Generally one would expect evidence of primarily parasympathetic ganglionic stimulation, leading to an increase in gastro-intestinal tone and motility and an increase in secretions. Dr. Batterman's paper will give a detailed account of the obscurities and disagreements involved in this overall generalization.

7. *General effects on the central nervous system:* When nicotine is administered to experimental animals in increasing doses, the effect on the central nervous system is that of initial mild stimulation, then marked stimulation (as manifested, for instance, by convulsive seizures) and finally depression. In man it is difficult to measure pharmacologically the effect on the central nervous system of the relatively small amounts of nicotine present as the result of smoking. However, on the basis of observations on animals, if this small amount of nicotine has any pharmacologic effect, it is probably one of stimulation.

8. *General effects on striated muscle:* The pharmacologic action of nicotine on striated muscle resembles very closely that produced by acetylcholine. Ordinarily the amount of nicotine present as a result of cigarette smoking is insufficient to elicit any skeletal muscle response. Overindulgence in smoking can lead to fibrillary twitchings which, incidentally, are the first skeletal muscle effects induced in animals given response-provoking doses of nicotine. As the amount of nicotine is increased, this stimulating effect gives way to a curare-like paralysis. Death from nicotine intoxication is due to this type of paralysis, to which the muscles of respiration seem particularly susceptible.

	Per cigarette
1. Dry solids (including so-called "tars")	40 mg.
2. Carbon dioxide	30 cc.
3. Carbon monoxide	15 cc.
4. Moisture (water)	10 mg.
5. Nicotine	3 mg.
Other volatile bases	0.25 mg.
6. Hygroscopic agent (glycerin or diethylene glycol)	3.00 mg.
7. Aldehydes	2.00 mg.
8. Formic acid	0.50 mg.
Benzoic acid	trace
Other volatile acids	1.70 mg.
9. Phenols	0.20 mg.
10. Cyanides	0.06 mg.

THE ALLERGIC RESPONSE TO TOBACCO*

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A survey of the literature would indicate that in view of the millions of smokers, tobacco rarely acts as an inhalant allergen or causes clinical evidence of hypersensitivity. Indeed, the relative importance of tobacco as an excitant which produces an allergic response is still in doubt, after much clinical and laboratory investigation. This is remarkable in the light of the repeated and intimate contact with tobacco of hypersensitive and potentially allergic individuals.

Nevertheless, the significant role that is played by the use of tobacco (particularly the smoking of tobacco) in the management of all types of allergy, and especially in respiratory allergies, must be seriously considered. Tobacco as a primary irritant may cause nasal congestion and obstruction, increased nasal discharge, pharyngitis, and even an impairment or a loss of the sense of smell. It is a common cause of cough as a result of its irritating action on the lower respiratory tract. This has been emphasized in an excellent manner by Waldbott (1), who points out the importance of the condition mistakenly termed "smoker's asthma" which, undetected for years as a clinical entity, is of relatively frequent occurrence in the nonallergic person. It is characterized by pain in the chest, frequent upper respiratory infections, dyspnea, wheezing, and constriction in the throat and upper air passages. One concludes that smoking is especially inimical to the health of the patient with bronchial asthma, a view strongly held by a group of Mayo Clinic workers (2), who state that no asthmatic person should ever smoke.

Tobacco is, further, a very significant factor as a secondary irritant in patients with allergic respiratory-tract conditions, particularly those with hay fever and bronchial asthma. Tobacco can also act as a primary sensitizer. It not only causes symptoms of the respiratory tract, but also of the skin (such as urticaria), of the cardiovascular system, and of the gastro-intestinal system, as well as allergic headache and contact dermatitis. It is significant, however, that even when one obtains a history very suggestive of hypersensitiveness or intolerance to tobacco, generally a simple chemical or mechanical irritation by the tobacco itself, or by the cigarette paper or combustion by-products of the materials mixed with the tobacco, is the more likely cause of the symptom complex.

Studies in the field of vascular disease, particularly peripheral vascular disease, have focused much attention on the etiologic, or at least contributing importance of tobacco. The pharmacologic reaction to smoking has been demonstrated by many observers to consist of a vasoconstriction with a resultant diminution in

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the blood flow and a consequent decrease in the skin temperature of the fingers and toes. It has also been demonstrated that similar increases in blood pressure and in pulse rate are obtained when nicotine in amounts equal to those theoretically absorbed in the smoking of one or two cigarettes is injected intravenously. The response was found to be the same in normal individuals as in those suffering from a peripheral vascular disease. Maddock (3) proved that these effects were the result of the action on the autonomic nervous system. He was able to abolish the vasoconstrictor effect by anesthetizing the nerve supply to the tested area. Mibashan (4) has observed what he considers to be seizures of "cardiac asthma" due to the sudden rise in blood pressure caused by oversmoking at night.

Harkavy (5, 6) questions the assumption that pathologic reactions occurring in some tobacco users are due solely to the pharmacologic action of smoking or nicotine, since many normal individuals do not show any symptoms, although they may smoke as much as those who have symptoms. He suggests, therefore, that the untoward reactions from tobacco may be associated with some nonpharmacologic mechanism which renders some persons more vulnerable than others. He considers allergy to be that mechanism.

Harkavy studied large numbers of smokers who were under treatment for thromboangiitis obliterans and for coronary artery disease. A high percentage of these smokers showed positive reactions to intradermal tests with tobacco extract. In some cases he was able, in addition, to demonstrate skin sensitizing antibodies by means of passive transfer.

Sulzberger (7, 8), who also favors this allergy concept, confirmed the positive reactions to skin tests with tobacco, but he was unable to confirm the findings of positive passive transfer reactions. Peshkin and Landy (9), however, obtained positive results in 72 per cent of transfer tests in those who gave direct positive intracutaneous reactions. These tests were performed on children (nonsmokers), and the incidence was much higher in the allergic than in the nonallergic subjects.

Trasoff and his co-workers (10) made large numbers of tests with tobacco in patients, both smokers and nonsmokers, allergic and nonallergic, who were suffering from thromboangiitis obliterans and coronary artery disease. The controls were individuals who had no demonstrable vascular disease. These observers found no relationship between sensitivity to tobacco and circulatory disorders and concluded that tobacco acts only as a toxic agent. Wescott and Wright (11), repeating these experiments, found the incidence of positive skin reactions to tobacco to be slightly higher in a control group of nonallergic smokers and in nonsmokers than in the group with vascular disease, thus confirming Trasoff's conclusion that tobacco acts only as a toxic agent.

Chobot (12), among others, was able to obtain positive skin reactions to tobacco extract in children and in nonsmokers. These investigators concluded that many of the so-called positive skin reactions to tobacco are nonspecific, since the individuals tested usually gave positive reactions to the pollens as well. The assumption was therefore made that hypersensitiveness to tobacco may be explained by the fact that tobacco and pollen possess a common chemical radical.

Rosen and Levy (13), however, reported the case of a child with a familial

allergic history, both maternal and paternal. There was a personal history of milk intolerance dating from birth, coryza and cough dating from the age of 6 months, and asthma dating from the age of 11 months. Passive transfer tests revealed moderately positive reactions to tobacco and also to house dust, kapok, milk and banana. The mother admitted that she had been an incessant cigarette smoker for many years. She smoked while nursing, feeding and diapering the child. Elimination of tobacco caused a rapid clearing of the infant's symptoms. There was a recurrence of symptoms only when the mother once again started to smoke. Although this might very well be a case of true hypersensitivity to tobacco, one must seriously consider that the tobacco smoke, or possibly the combustion by-products of the cigarette paper, was acting as a respiratory irritant in this particular patient.

That tobacco smoke itself may be the allergenic excitant is also disputed. Vaughan (14) has demonstrated that patients not sensitive to tobacco per se may be sensitive to its smoke. He recommends that testing should be carried out with extracts prepared by bubbling tobacco smoke through Coca's fluid. Urbach and Gottlieb (15) concur in this view when they discuss tobacco smoke as the inhalant cause of asthma. The contrary view is held by Unger (16), who feels that true allergy to tobacco smoke is very uncommon, since he was unable to obtain any positive reactions by intracutaneous testing of smokers as well as nonsmokers, using an extract of tobacco smoke prepared after the method of Pipes (17).

Many reports of so-called hypersensitiveness to tobacco are actually irritability to the nonspecifically disturbing factors in the tobacco itself, in the tobacco smoke or in the combustion by-products of the paper. It has been noted that on occasion one type of cigarette will cause allergic symptoms, which are relieved when a different brand of cigarette is smoked. This may be explained by the fact that each familiar kind of cigarette contains a different type of compound to provide the flavor and aroma which are the characteristics of that particular brand.

Vero and Genovese (18) point out that in some instances, particularly among cigar smokers, the allergen is to be found not in the untreated tobacco leaves, but in those leaves that have undergone curing and fermentation processes. In other cases, the hypersensitiveness is in relation to the gum arabic, gum tragacanth, Jamaica rum, glucose syrup, or molasses used in the preparation of cheap cigars.

Tobacco often contains appreciable amounts of arsenic, originally placed in the soil to combat insects. It may well be that this arsenic when ingested by the tobacco user, be he a cigar or cigarette smoker or a tobacco chewer, can cause a multitude of skin manifestations. Chief among these are the acute and chronic dermatitides, and the polymorphous erythemas. Less frequently encountered are the bullous or erysipeloid exanthems, the exanthems (stomatitis), fixed drug eruptions, urticaria, angioedema, erythema exudativum multiforme, erythema nodosum, purpura, and drug eruptions of the acneform, nodular, ulcerous, pemphigoid or vegetative types. Aside from these skin manifestations other

reactions to arsenic which are commonly encountered are asthma, rhinopathy, nausea, malaise, attacks of abdominal cramps and diarrhea, bleeding from the urogenital tract, granulocytopenia, lymphadenopathy and joint swelling and pain (19).

Newman (20) has pointed out that cheilitis or circumoral or finger dermatitis may develop in cigar and cigarette smokers, because of the action of certain ingredients added to the tobacco product, such as diethylene-glycol. Link has reported such reactions caused by sensitivity to the cigarette paper. Rappaport and Hoffman (21) found that the acrolein combustion products of glycerine in cigarettes were the cause of the urticaria suffered by some smokers.

Surely tobacco is an important allergic excitant when it assumes the role of a contactant, particularly among handlers of tobacco on the farm and in the factory, and also among dealers. In addition to many dermatitides reported, Mibashan (4) has observed spasmodic rhinorrhea, prurigo, urticaria and angioedema appearing in tobacco workers who had been, allegedly, free of such manifestations before beginning work in the tobacco factories. Unger (16) has found it necessary to institute, and has successfully employed, tobacco hyposensitization in workers in the tobacco industry.

Possibly rather more important than the antigenicity of tobacco is the clinicosocial problem presented by smoking. Raymond Pearl (22) in 1922 found the life span to be significantly shorter for smokers than for nonsmokers, without limiting the effect of any one cause of death. Today one is confronted with the relationship between smoking and carcinoma of the lung. Statistics show that the mortality from bronchogenic carcinoma has increased fifteen-fold in the twenty-five years between 1922 and 1947. This increase has been recorded in all the countries of the world, with the exception of Iceland where cigarette consumption has been, until just recently, negligible. Observations have shown that after the age of 45 years, carcinoma of the bronchus is fifty times more likely to develop in persons who smoke 25 cigarettes daily than in those who do not smoke (23). Disturbing also are the studies in genetics which indicate the possibility that smoking by women in the child-bearing period may seriously interfere with the normal reproductive functions and with lactation (24).

Whether one accepts or rejects the concept of allergy to tobacco as the etiologic agent in the production or aggravation of vascular diseases, be it peripheral vascular disease, coronary artery disease or even vascular headache, there can be no question as to the importance that tobacco plays as a toxic agent or as primary or secondary irritant.

In the treatment of respiratory allergies, particularly asthma, the avoidance of smoking cannot be stressed strongly enough. The patient must be made to understand that smoke of any type is irritating and not soothing to the mucous membranes. The cough, bronchitis and bronchospasm which are induced by smoking should be considered nature's warning to avoid or to expel the irritating effects of this noxious agent. All patients with asthma have some degree of bronchitis, as manifested by inflamed, swollen mucous membranes and by the associated bronchospasm. These inflamed membranes are extremely sensitive to such

irritants as smoke, dust, fumes, cold air, and strong pungent odors. Smoking is one of the most common sources of bronchial irritation and it invariably increases cough and asthma when continued for any length of time. Certainly no patient with asthma should irritate his inflamed membranes with smoke just because tests for allergy to tobacco have given negative findings. It is not at all uncommon to observe that satisfactory results in the management of the patient with a respiratory allergy may depend on the complete elimination of tobacco.

CONCLUSIONS

Tobacco may act as an allergen more frequently than suspected. Its effect. however, would seem more often to be the result of its toxic and irritating nature. In allergy, it plays a more readily established role among individuals who work with tobacco than in those who smoke. Whether it be a specific allergic excitant or a potent nonspecific irritant, tobacco should be avoided by all persons who suffer from respiratory or vascular disease.

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USE OF VASODILATOR DRUGS IN THE TREATMENT OF DIABETIC ARTERIOSCLEROSIS OBLITERANS*

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Arteriosclerosis obliterans, the most common complication of diabetes mellitus, frequently leads to gangrene (1). The realization that in many of these patients there is a large element of vasospasm has given us a more conservative therapeutic approach, and has saved some patients from undergoing amputation of a limb (2, 3).

The most certain method of abolishing vasospasm is the performance of a lumbar sympathectomy (4, 5, 6). This operation has the advantage of being permanent, and affecting one or two extremities without causing generalized vasodilatation. It has the disadvantage of being a major surgical procedure which requires considerable skill. Since these patients are usually poor surgical risks and have an average life expectancy of less than five years, a few operative deaths are inevitable. After operation some patients have severe pain at the site of the incision, or have postural hypotension. If the vasospastic element is small, or if the sympathetic nerves are incompletely removed, the results are poor. At the present time our policy is to urge this form of surgery for all patients with pain or gangrene, and to suggest it to those with moderate symptoms. It should always be a bilateral procedure unless the patient has had a unilateral high amputation, in which case the operation should be performed on the other side in order to protect the remaining foot.

There remains a large group of patients who either refuse surgery, or whose symptoms are too mild or physical condition too poor to justify it. Many forms of therapy have been used to aid these patients.

Applying heat to the upper part of the body will produce reflex vasodilatation in the legs. This is impractical as a therapeutic procedure, but the principal of avoiding general body chilling is a good prophylactic measure. Applying heat directly to the affected limb causes local increased oxygen demand, and tends to aggravate the ischemia.

Alcohol is the oldest known vasodilator, but unfortunately its caloric content and its effect upon the cerebral cortex limit its usefulness in patients with diabetes.

Histamine has been frequently used in the past because of its direct action in dilating the small arterioles (13). However, the side-effects, such as increased gastric acidity, migraine headaches and vasomotor-rhinitis, make it of little practical use.

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Nicotinic acid is a weak vasodilator with a transient unpredictable action that has made it of little therapeutic value (7).

Roniacol,[1] the alcohol of nicotinic acid, is slowly broken down in the body to release free nicotinic acid (8–12). The dose varies from 50 to 200 mg. three to four times a day. Some of the poor results which we obtained from the earlier use of this drug were later found to be due to inadequate dosage. The only toxic effects are flushing of the face and, rarely, nausea. It is apparently the safest vasodilator available and should be used in the larger dosages, if necessary, before any decision is made regarding its effectiveness. We used it in 15 patients with some improvement in all but 3.

Several drugs directly antagonistic to epinephrine have been developed recently. Most of these are of little clinical value, because they require parenteral administration and have only a transient effect. Priscoline[2] has been used orally (14, 15), intramuscularly, intravenously (16, 17) and intra-arterially (18) for about eight years, so that its value is well established. It is a combination of the histamine nucleus and the epinephrine nucleus, and therefore has a direct vasodilatory effect and also produces a peripheral adrenergic and sympathetic block (19). The oral dosage varies from 25 to 50 mg. every three to four hours. The drug starts to act in an hour and its effect is prolonged for several hours, with a tendency to be cumulative. In full therapeutic doses the skin is flushed and there are chilly sensations. Aggravation of peptic ulcer and precipitation of coronary thrombosis have been reported; other toxic effects are similar to those of histamine. We have used Priscoline in 25 patients and have noted no serious toxic effects; there was some improvement in all but 4 patients. It has been effective in increasing the warmth of the feet, relieving ischemic pains, and aiding the healing of ulcerations.

Regitine,[3] the newest vasodilator, is similar to Priscoline except that it has two instead of one benzene ring. This makes it a more potent adrenergic and sympathetic blocking agent, with little direct effect on the walls of the blood vessels (20). Regitine is best known as a diagnostic agent for pheochromocytoma. When given by mouth in a dosage of 50 to 100 mg. every two to six hours, it causes a prompt vasodilatation which is often more pronounced than that obtained with Priscoline, and usually is associated with fewer unpleasant side-effects. The toxic effects noted are tachycardia, apprehension, and gastro-intestinal disturbances. We have had some improvement in 9 of the 10 patients treated with this drug.

There are so many variable factors in peripheral vascular disease that proper evaluation of any drug is very difficult. The results of experiments made by measuring the skin temperature changes after a single intravenous injection of a fixed dose (21) cannot be applied to patients being treated with repeated oral administration of variable doses. Moreover, it has been shown that the sclerotic

[1] Roniacol, (NU-2121) β-pyridyl carbinol, was supplied by Hoffman-La Roche, Inc., Roche Park, Nutley 10, New Jersey.

[2] Priscoline, 2-benzyl-4, 5-imidazoline hydrochloride, was supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[3] Regitine, (C7337) 2-[N′-p-tolyl-N′-m-hydroxyphenylaminomethyl]-imidazoline, was supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

process in patients with diabetes is often an endarteritis obliterans that affects the terminal arterioles. This dysfunction may cause a very low skin temperature, although the deeper circulation may be adequate (22). Therefore, it is necessary to try each drug in each patient in full therapeutic and subtoxic doses for several weeks before conclusions can be drawn. Such observations have been made in too few patients to enable us to say which is the drug of choice at this time. One works best on some patients and another works best on others. The possibility of using them in combination or in succession is worth considering.

SUMMARY

In the treatment of diabetic arteriosclerosis obliterans Priscoline is an effective standardized vasodilator, and should be tried first. If the response is poor in full therapeutic and subtoxic doses, then Regitine should be used. The effect of Regitine closely approximates that of a sympathectomy and may be dramatic. Roniacal is the safest vasodilator, but since its effects are so variable it should be reserved for use when results with the other drugs are unsatisfactory.

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INTRACTABLE ANGINA PECTORIS: TREATMENT WITH FRACTIONAL DOSES OF RADIOACTIVE IODINE*

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Treatment of intractable angina pectoris is a major problem. The patient is incapacitated and apprehensive. He wanders from physician to physician hoping to obtain some relief.

The emotional upheaval coincident with each failure, especially after seeing renowned cardiologists, often has the effect of aggravating the condition. Anything affording relief will, in turn, ease emotional stress in these patients—the very stress which, in many instances, may act as a trigger mechanism.

Coronary insufficiency as a cause of angina pectoris has become so ingrained in our way of thinking that it tends to overshadow many other conditions which may give rise to, or aggravate this syndrome.

The presence of a hiatal hernia deserves more consideration as an important factor in angina pectoris. In some instances it may be the sole cause of attacks which simulate angina pectoris of coronary origin, even to the electrocardiographic changes; moreover the discomfort or pain is relieved by nitroglycerine. (A future publication will deal with this phase of the subject.)

Gallbladder or pancreatic disease may be responsible for attacks which are difficult to distinguish from Heberden's angina, particularly in individuals in whom coronary disease has left the pain pathways hypersensitized. Pain may also be referred to the precordium from pathologic processes in the neck, pleura, lung and mediastinum, from arthritic disorders in the cervico-thoracic spine and cervical ribs, or from occasional radiculitis.

Angina may be caused and more frequently aggravated by sensitization to nicotine, by coffee or by food allergies. It may be encountered as fatigue-ache following prolonged rapid heart action in attacks of paroxysmal tachycardia. Unless carefully questioned, patients fail to convey this particular point in the history. Hyperthyroidism, severe anemia, and aching of the overworked heart in chronic hypertension are important contributory factors. Angina pain occurs in aortic stenosis and insufficiency and in aortitis of rheumatic, syphilitic and mycotic origin, if the process involves the coronary orifices.

Gastro-intestinal disorders leading to abdominal distention and consequent forcing of the diaphragm into the left thorax, may cause a crowding of the mediastinum. We have seen the heart slightly twisted on its longitudinal axis and have demonstrated changes in position roentgenologically, following the introduction

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and removal of air from the stomach. Such displacement of the heart may, in vulnerable cases, interfere with the coronary flow and cause anginal attacks. Many believe that stretching of the peritoneum may be a trigger mechanism in this type of angina pectoris.

Since, therefore, angina pectoris is a symptom-complex which is encountered in many pathologic states, it is imperative that the underlying cause or causes be ascertained before resorting to *any* form of therapy except that for symptomatic relief.

Lowering of metabolic rate—the goal of therapy

After every attempt to correct pathologic lesions which may cause or contribute to anginal attacks has failed, lowering of metabolic activity should be considered as a therapeutic approach. It has long been known that by lowering the metabolic requirements of the body, frequency and severity of anginal attacks are favorably influenced. This decrease in basal metabolism has been accomplished by roentgen irradiation of the thyroid gland, by thiouracil and other antithyroid drugs, and by partial or total thyroidectomy.

The irreversibility and risk associated with thyroidectomy in patients with angina have made this approach to the problem too drastic. The results, however, have served the useful purpose of emphasizing that anginal attacks may be controlled by depressing metabolic activity. Thiouracil, and all other antithyroid drugs used over a prolonged period, carry with them the danger of agranulocytosis (1). In most cases the results with this form of therapy are slow, and lack uniformity (2). Nevertheless, propylthiouracil, methylthiouracil and iodothiouracil (Itrumil) are useful adjuncts in the treatment of selected cases of angina pectoris.

The advent of radioactive iodine (I^{131}) has made available a new, effective and easily controlled therapeutic agent. With the use of I^{131} it is possible to produce desired degrees of hypothyroidism with relative safety. There is the additional advantage that hypothyroidism so induced is *self-reversible* provided the dose is not too excessive. Administration entails no discomfort and the patient is hardly aware of the fact that the "white cocktail" contains the drug.

The degree of thyroidal isotopic activity may be fairly accurately determined by the Geiger counter, without discomfort to the patient.

METHODS

Clinical material

This report is based on our experience with 32 patients who were selected because of *intractable angina pectoris*, and in whom all known methods of therapy failed. Some of these patients took as many as 20 nitroglycerine tablets daily. Their ages ranged from 42 to 78 years. Twenty-four were euthyroid, judging from physical examination, basal metabolic rate and thyroidal isotope uptake of a tracer dose of I^{131}. Five were hypothyroid as indicated only by the basal metabolic rate and isotope uptake, and 3 were hyperthyroid with increased isotope uptakes and suggestive clinical evidence though the basal metabolic rates were within normal limits.

The classification of patients, based on the thyroidal uptake of a tracer dose of I^{131} was as follows:.

The percentage of thyroidal I^{131} uptake did not always parallel the basal metabolic rate in the same individual. We found that a low basal metabolic rate or a low level of serum protein-bound iodine was no contraindication to employing I^{131} therapy, nor did they influence the response. A low basal metabolic rate or a low thyroidal uptake of I^{131} tracer did, however, influence us in determining the size of the initial and subsequent therapeutic doses.

Personnel and equipment

An "Isotope Committee" approved by the Atomic Energy Commission consisted of a radiologist specially trained in isotope therapy, an internist, an endocrinologist and a radiation physicist. The committee worked as a team in selection of patients and in administration of the isotope.

The equipment consisted of a Geiger-Müller scaler and a Geiger tube, used for determining the I^{131} radiation; an electrometer for assaying the isotope; lead bricks for shielding it; a beta-gamma survey meter; a minometer and a "cutie-pie," required for safeguarding personnel; and pipettes and other glassware, required for measuring and administering the isotope.

Preparation of patients

To obtain a correct reading of the thyroidal I^{131} uptake following the tracer dose it is essential that no medication which affects thyroid activity be administered for at least eight weeks prior to the test.

Such drugs include the thiouracils, and iodine in any form—topical applications, iodides, thyroid, thyroxine, iodothiouracil, and iodine-containing substances used in roentgenography such as Telepaque, Pantopaque, Diodrast, Lipiodol or Menophen, as well as intravenous and intramuscular preparations containing iodine.

Dosage of I^{131}

Depending upon the percentage uptake of the tracer dose and the severity of anginal symptoms, the patient is given 5 to 15 millicuries of I^{131}. Larger doses have been employed in some clinics (3). We found that it is best to start with a small dose, since it can easily be repeated. If the tracer uptake is high the initial therapeutic dose should not exceed 5 millicuries. Masked hyperthyroidism is often discovered in patients whose B.M.R. is normal. As mentioned before, 3 of our series of patients has a normal B.M.R. with an isotope uptake ranging from 50 to 75 per cent. In such instances it is particularly important to start with a small dose (contrary to what one would expect) in order to prevent a thyroid crisis. At the end of eight weeks the patients are re-evaluated, at which time a tracer dose of 100 microcuries of I^{131} is administered. If indicated, a second fractional therapeutic dose of I^{131} may then be given.

Uptake below 10 per cent	Hypothyroid
Uptake, 15 to 40 per cent	Euthyroid
Uptake above 50 per cent	Hyperthyroid

RESULTS

Four of the 32 patients with intractable angina experienced complete remission of symptoms with one dose of I^{131} (average, 10 millicuries). Slight evidence of depressed thyroid activity was found in this group following treatment.

Ten patients had some relief following one dose of I^{131} and complete remission of symptoms following a second dose. These patients became definitely hypothyroid. The average total dose was 22 millicuries.

Twelve patients experienced some relief of symptoms following two courses of I^{131} but showed minimal evidence of depressed thyroid activity. The two doses averaged 16 millicuries. A third dose has been administered to this group but re-evaluation has not yet taken place.

Six patients had no alleviation of symptoms following two courses of therapy with an average total dose of 18 millicuries. This group showed minimal evidence of depressed thyroid activity. A third dose has been administered but re-evaluation has not taken place.

Three patients of those who were completely relieved of anginal attacks were very uncomfortable because of symptoms of myxedema such as stiffness of the hands, stiffness and hardness of the facial skin, lethargy, rapid gain in weight, marked puffiness of the eyelids and striking changes in facial appearance. These symptoms were controlled to a limited extent by administration of thyroid. We were surprised to find how little thyroid these patients could tolerate. In 1 of the 3 patients angina pectoris recurred during the administration of $\frac{1}{4}$ grain of thyroid per day. In the other 2, there was a return of symptoms during administration of $\frac{1}{2}$ grain daily. Small divided doses, such as $\frac{1}{20}$ grain three or four times daily were fairly well tolerated.

Although radioactive iodine has been shown to be a promising therapeutic agent in the treatment of intractable angina pctoris, we also paid attention to the underlying etiologic factors and carried out such therapy as the reduction of hypertension by the parenteral and oral use of methonium compounds and *Rauwolfia serpentina*. In cases of atherosclerosis we stressed self-administration of Polypancrine (a polyextract of the pancreas prepared in our laboratories) or Pancromone, either daily or every other day. With alleviation of the attacks, patients accept the therapeutic regimen with more confidence and submit to the guidance of the physician in the best cooperative fashion, thus insuring better end-results.

Several of the patients, in addition to attacks of angina, had been experiencing frequent attacks of paroxysmal auricular tachycardia or paroxysmal auricular fibrillation. Following I^{131} therapy, there was complete cessation or marked alleviation of the attacks, both in severity and frequency.

Since our experience with this series of 32 cases, we have found that a small dose of 5 to 10 millicuries of I^{131} repeated over intervals of two to three months without producing pronounced hypothyroidism seems to be a valuable adjunct in the treatment of any form of cardiac failure, anginal or congestive. This approach definitely enhances the effectiveness of other therapeutic measures which previously failed to alleviate anginal seizures in the same patient. We

have, therefore, concluded that it is best to use a combination of small doses of I^{131} with prevailing forms of therapy.

SUMMARY

Thirty-two patients with intractable angina pectoris were treated with fractional doses of radioactive iodine. Fourteen of these patients experienced complete remission of symptoms; all of them showed signs of depressed thyroid activity.

The degrees of relief from anginal seizures in many instances seemed to be in direct proportion to the decrease in thyroid activity obtained with the use of I^{131}.

Hypothyroidism, as shown by a low basal metabolism and serum protein-bound iodine level, is not a contraindication to isotope therapy.

Therapy with fractional doses of radioactivive iodine opens a new avenue of approach which shows promise in the treatment of intractable angina pectoris. Ease of administration, reversibility of action and relative safety warrant its use in patients who have failed to respond to other forms of therapy.

A combination of prevailing forms of therapy with I^{131} is more effective than either type of treatment alone.

It is of the utmost importance, despite alleviation of symptoms by isotope therapy in many instances, that the underlying cause or causes of the anginal attacks be treated in the most effective way.

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STUDIES COMPARING THE EFFECTS OF CERTAIN TESTOSTERONE ESTERS IN MAN*†

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INTRODUCTION

This is a brief preliminary report of an investigation which will be published in detail when it is completed. The study was initiated for two immediate purposes: 1) to compare in man the relative activity of certain testosterone esters in terms of the duration and the amount of their protein-anabolic and urinary 17-ketosteroid-augmenting properties; and 2) to provide a basis upon which to select the most suitable compound for the prolonged induction of these metabolic manifestations in man. In addition, this investigation has two long-range objectives: 1) to determine whether these testosterone esters and certain of their metabolic properties exhibit a dose-response relationship in the human; and 2) to create a background of observations against which new potential therapeutic agents may be evaluated for these metabolic properties. Testosterone induces in man anabolism of protoplasm as indicated by retention of nitrogen, phosphorus, potassium and sulfur in the proportions that exist in protoplasm during metabolic balance studies (1, 2). This steroid is metabolized and excreted as urinary 17-ketosteroid compounds, with exogenous testosterone adding an increment to the metabolites that arise from endogenous sources of the hormone (3).

MATERIAL AND METHODS

In the present study, the duration and the amount of nitrogen retention, of 17-ketosteroid excretion, and of clinical response have been determined and compared for testosterone propionate (TP) in oil, testosterone propionate (TP) in aqueous suspension, testosterone cyclopentylpropionate (TCP) in oil, and testosterone phenylacetate (TPA) in aqueous suspension in 5 hospitalized women (aged 46, 66, 69, 77 and 81) with osteoporosis of the postmenopausal and senile types, and 8 out-patient men (aged 22, 28, 29, 30, 32, 33, 43 and 51) with hypogonadism.

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Nitrogen balance studies were carried out by standard procedures (2). The amount of nitrogen (Kjeldahl method) was determined in the diet (every eighteen days), in the feces (six-day collections), and in the urine (two-day, three-day or six-day collections). The neutral 17-ketosteroids in the urine were determined by hydrolysis, extraction with carbon tetrachloride, and measurement of the Zimmermann reaction with aqueous potassium hydroxide through a green filter against a dehydroepiandrosterone standard.

In the chemical studies, the testosterone esters were administered as single intramuscular injections of amounts equivalent to 244 mg. of testosterone. In each instance the effect of TCP or of TPA was compared with that of the appropriate preparation of TP in the same patient. To date, each compound has been studied in at least 2 individuals.

RESULTS OF METABOLIC STUDIES

The results will be presented in detail in the final publication. In each instance, the nitrogen balance and the 17-ketosteroid excretion were determined during control periods ranging from twelve to eighteen days; then the testosterone ester to be evaluated was administered, and the nitrogen retention and 17-ketosteroid excretion were followed until the patient again was in equilibrium

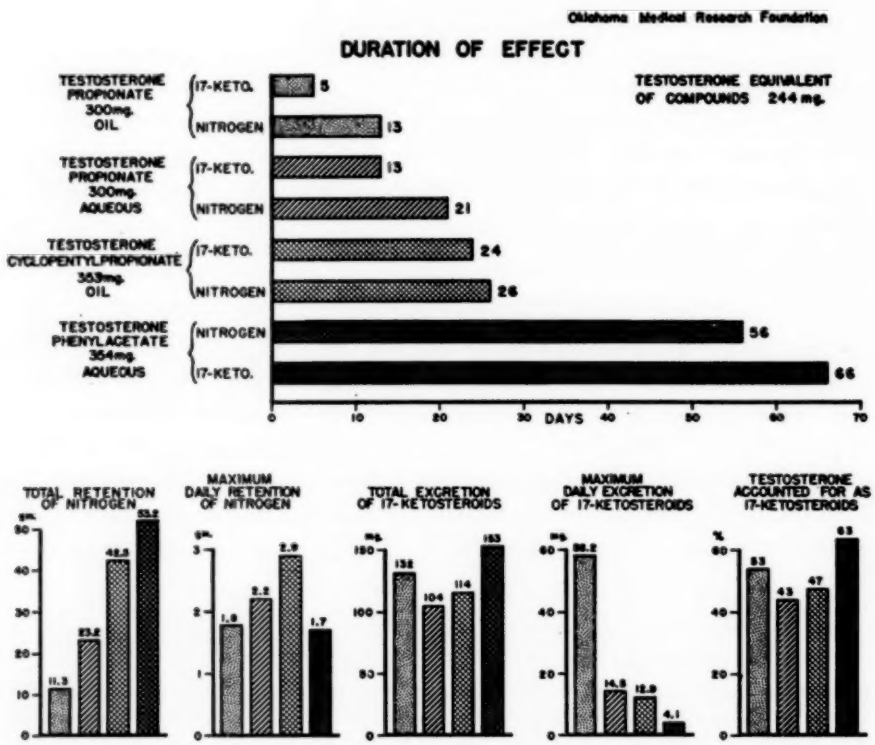

FIG. 1. Duration and amount of protein-anabolic and urinary 17-ketosteroid-augmenting properties of 3 testosterone esters (testosterone propionate, testosterone cyclopentylpropionate, and testosterone phenylacetate) in man, as determined from nitrogen balance and urinary excretion studies.

for a period of twelve to eighteen days. At this point, a second testosterone ester was administered and the entire procedure repeated. In order to determine the net response to an injected steroid, the control periods immediately preceding the administration were averaged and the balances of retention or excretion were corrected for these control averages. Subsequently, the data for all individuals given a particular compound were averaged. In the case of the 17-ketosteroid excretions, the standard deviations of the values during the control period were calculated, and no value was considered to be a significant increase following the administration of a testosterone ester unless the amount corrected for the basal 17-ketosteroid excretion exceeded two times the standard deviation of the control basal 17-ketosteroid excretion. No allowance was made for any inhibition of endogenous testosterone production which might have occurred as a result of the injection of the testosterone ester.

Figure 1 summarizes the duration of effect of the compounds tested, in terms of the average duration observed in the study of at least 2 patients for each compound. The effect of TP in oil had a duration of five days as determined by the 17-ketosteroid excretion, and of thirteen days as determined by the nitrogen retention. The effect of TP in aqueous suspension had a duration of thirteen days as determined by the 17-ketosteroid excretion, and of twenty-one days as determined by the nitrogen retention. The effect of TCP in oil had a duration of twenty-four days as determined by the 17-ketosteroid excretion, and of twenty-six days as determined by the nitrogen retention. The effect of TPA in aqueous suspension had a duration of fifty-six days as determined by the nitrogen retention, and of sixty-six days as determined by the 17-ketosteroid excretion.

Figure 1 also shows that the total retention of nitrogen increased in direct proportion to the duration of the effectiveness of the compound. The total amount of the 17-ketosteroid material excreted, however, was approximately the same, regardless of the duration of the effect of the compound. The maximum daily retention of nitrogen increased directly with the increase in duration of the effect up to a point, then decreased in the case of the most long-acting compound. It is possible that a still larger dose of TPA could be used by single injection without exceeding the limits of protein anabolism. The maximum daily excretion of 17-ketosteroids occurred during administration of the compound with the shortest duration of effect, and decreased as the duration of effectiveness increased. Approximately half of the testosterone injected was accounted for by the increment in the 17-ketosteroid excretion, regardless of the duration of action of the compound.

Some additional observations not shown in Figure 1 deserve mention. It has been demonstrated previously (4) that 17-methyltestosterone is not excreted in the urine as 17-ketosteroid compounds, and frequently causes a fall in the 17-ketosteroid excretion, probably by inhibiting endogenous testosterone production. An attempt was made to utilize this fact to decrease and stabilize the basal 17-ketosteroid excretion, and thus make it easier to follow the 17-ketosteroid metabolites of the injected testosterone esters. Three hypogonadal out-patient men were given 75 mg. of 17-methyltestosterone by mouth daily for two or more

weeks, both before and throughout the period of observations following the injection of TP or TCP. Spot determinations of the 17-ketosteroid excretion were made on aliquots of 24-hour urine collections. In contrast to what had been anticipated, the 17-ketosteroid values obtained during the administration of methyltestosterone orally in this dosage, and prior to the injection of testosterone esters intramuscularly, failed to show convincing evidence of suppression of excretion. After the injection of the testosterone esters, the increment of urinary 17-ketosteroid excretion appeared to be the same as that which was obtained when no 17-methyltestosterone was administered simultaneously.

RESULTS OF CLINICAL STUDIES

Five additional men have been observed clinically. All of them were eunuchoid congenitally; their ages were 22, 28, 29, 33 and 43 years, respectively. These men had received androgen therapy for varying periods of years, and required an average maintenance dose of 40 mg. of testosterone propionate weekly, or its equivalent. Two of them were equally comfortable on 100 mg. of TCP given once per month; one required 100 mg. of TCP every three weeks; and another preferred 50 mg. of TCP every two weeks. One man required 50 mg. of TPA every four weeks; this latter patient had previously been maintained satisfactorily on 25 mg. of 17-methyltestosterone daily by mouth. These clinical observations are in accord with the metabolic studies.

Attention should be called to the fact that the preparations in aqueous suspension caused local pain, swelling, and tenderness for several days; then the reaction subsided. No residual effects were detectable in the patients at the time when the subsequent injections were given.

DISCUSSION

It has been recognized for several years that aqueous suspension of crystals of testosterone and other steroids produce a local reaction. Since the injections of the preparations herein reported would be administered less frequently because of the prolonged action, the local reaction may not constitute an important obstacle to the use of aqueous suspensions therapeutically. Furthermore, preparations in oil have been criticized because the deposits of oil in the muscle are not always quickly absorbed.

The failure of 17-methyltestosterone to suppress endogenous 17-ketosteroid production may have been due to the administration of an insufficient dose, to the type of patient to whom the medication was given, or to the level of 17-ketosteroid excretion of these patients when they were not receiving therapy.

Masculinization was not observed in the hospitalized women treated with these preparations. However, the clinical response of eunuchoid males was adequate, with doses of the magnitude used in this study.

The testosterone esters with longer duration of action produced only a moderate and sustained increase in 17-ketosteroid excretion, which suggests efficient utilization of the injected steroid by the body. In contrast, the shorter-acting esters, such as TP, produced immediately a marked excretion of 17-ketosteroid

material, which suggests wastage of the injected compound. In spite of this difference in the pattern of excretion, the total amount of 17-ketosteroids produced by the various esters was approximately the same, hence a measurement of the total amount of 17-ketosteroids excreted following the injection of a testosterone ester gives no indication as to the total amount of protein anabolism that has occurred.

The results of the observations herein reported confirm and extend those of other investigators who have studied some of these testosterone esters (5–12).

SUMMARY AND CONCLUSIONS

A preliminary report is presented of a study still in progress concerning the relative activity of certain testosterone esters. To date, the following have been studied: testosterone propionate (TP) in oil, testosterone propionate (TP) in aqueous suspension, testosterone cyclopentylpropionate (TCP) in oil, and testosterone phenylacetate (TPA) in aqueous suspension, all administered as single intramuscular injections of amounts equivalent to 244 mg. of testosterone.

These compounds have been compared in terms of: a) the duration and the amount of their protein-anabolic effect as determined from nitrogen balance studies on 3 women with osteoporosis; b) the duration and the amount of their urinary 17-ketosteroid-augmenting effect as determined on the 3 osteoporotic women during the balance studies and on 3 hypogonadal male out-patients; and c) the amount of steroid required in a given period of time to maintain full clinical response in 5 congenitally eunuchoid males.

The chemical studies showed that the compounds had the following duration of effect: TP in oil—five to thirteen days; TP in aqueous suspension—thirteen to twenty-one days; TCP in oil—twenty-four to thirty-six days; and TPA in aqueous suspension—fifty-six to sixty-six days.

Total nitrogen retention was directly proportional to the duration of the effect; whereas total 17-ketosteroid excretion was approximately the same, regardless of the duration of the effect. The maximum daily nitrogen retention was directly proportional to the duration of the effect up to a point, and then decreased; whereas the maximum daily 17-ketosteroid excretion was inversely proportional to the duration of the effect.

It is suggested that the longer-acting testosterone esters are not wasted by being immediately excreted in the urine as 17-ketosteroids, in contrast to the shorter-acting esters such as TP.

In the clinical studies, the testosterone esters appeared to have approximately the same relative and absolute duration of effect as was shown by the chemical studies.

The simultaneous administration of 17-methyltestosterone, which theoretically should have inhibited the endogenous 17-ketosteroid production, did not do so and also did not appear to alter the 17-ketosteroid response to TP in oil or to TCP in oil.

On the basis of increased duration and intensity of effect, TCP and TPA

appear to be better therapeutic agents than TP for the management of conditions in which prolonged testosterone administration is desired.

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RECENT ADVANCES IN SURGERY*

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Surgical progress in recent years may be evaluated in three ways; first, by the reduction in operative mortality and morbidity; secondly, by the extension of the field of surgical endeavor; and, thirdly, by the more prompt and complete rehabilitation of the patient. Recent advances will be considered in the phase in which their impact has been greatest.

REDUCED OPERATIVE MORTALITY AND MORBIDITY

The availability of a wide variety of safe, stable, antibacterial drugs of reliable potency is of prime importance in this category. These drugs have largely eliminated many surgical complications which were commonplace even ten years ago. Among these are postoperative subphrenic, subhepatic and intra-abdominal abscesses; spreading pyoderma of the anterior abdominal wall; fecal fistula after appendectomy; abscess following perforated diverticulitis of the sigmoid; carbuncles; gas gangrene; pylephlebitis; and septicemia. Today these complications are not only rare, but respond to therapy more readily when they do occur. The antibacterial drugs, in addition to reducing complications, have altered surgical technique. Prolonged drainage of the contaminated peritoneal cavity is rarely practiced today; its place has been taken by intraperitoneal instillation of large amounts of antibiotic solutions, and closure without drainage.

Surgery of the colon has probably received the greatest benefit from the antibacterial agents. Operative mortality has dropped steadily. In our series we have had 1 death in the past consecutive 120 resections. Of these 120 patients only 3 required a preliminary colostomy and only 4 were left with a permanent colostomy. All anastomoses were of the open type, using interrupted stainless-steel wire sutures. Wound infection was a rarity and there were no cases of disruption of the anastomosis. Reduction of the intestinal bacterial flora with oral antibiotics has been of great value. We discontinued the use of nonabsorbable sulfones several years ago after observing that many patients excreted the tablets exactly as ingested, not even softened by their trip. Since the report of Dearing and Heilman (1) in February 1950, we have used Aureomycin to prepare the bowel, with very satisfactory results. The routine substitution of stainless-steel wire for the more commonly used gastro-intestinal suture material deserves mention (2). For several years we have employed it exclusively (⁂36 or ⁂37 wire interrupted sutures, in two rows) and have been greatly impressed by its advantages. This wire (known colloquially as "angel hair" or "frog's lanuga") is,

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much finer than any other suture material of comparable strength and makes possible a most delicate and meticulous technique. Stainless steel is inert, so that healing proceeds without delay; it also lacks capillarity, so that the sutures remain in place indefinitely. Following low anterior resections, the shiny wires may be visualized or palpated along the suture line years after the operation. The edematous polypoid granulation tissue so commonly seen along a silk or cotton suture line is conspicuous by its absence. Our experience with this technic permitted us long ago to discontinue any type of nasogastric suction in elective colon resections. The patients are started on oral liquids the morning after operation and paralytic ileus is a rarity.

We also use stainless-steel wire in the outer suture row, after gastrectomy and in the closure of the duodenal stump. Over a period of years, no duodenal stump closed with steel wire has re-opened. The lack of edema at the gastrojejunal stoma permits early emptying of the gastric pouch, so that in the past two years no Levin tube has been required preoperatively in gastric surgery and only 3 of 60 patients have required postoperative intubation. This reduces the incidence of pulmonary complications and helps to maintain a normal electrolyte pattern, especially in very hot weather when sodium and chloride depletion may become troublesome.

Preoperative preparation is probably the next most important factor in reducing operative mortality and morbidity. In elective surgery the principle "Is the patient strong enough to undergo surgery?" has changed to "Is the patient as well prepared as possible?" Thus, preexisting anemia, protein and electrolyte deficiency and diminished blood volume must be corrected prior to operation. Part and parcel of this concept is the prompt, adequate replacement of operative blood loss. In this regard, quantitative measurements of blood loss have contributed a great deal to the operative management. The blood loss during major surgery will usually exceed the surgeon's estimate by from 100 to 300 per cent, unless he has been educated by measurement techniques. If adequate replacement is carried out, the patient enters the convalescent period in optimum condition.

A better understanding of surgical physiology, the reaction of the organism to the stress of surgery, the selective excretion of potassium and retention of sodium during the postoperative period, the dangers of salt intoxication and a recognition of endocrine function have all helped to smooth the course of a patient undergoing surgery.

EXTENSION OF THE FIELD OF SURGICAL ENDEAVOR

It is customary, upon the advent of each new therapeutic agent, for someone to predict that surgery will soon be reduced to the repair of congenital and traumatic defects. However, the converse has been true, until today surgical therapy must be nearing its ultimate limits—an opinion incidentally which was also expressed by Ambrose Paré in the sixteenth century. Advances in cardiac surgery, the newest and most exciting field, will be dealt with by other speakers on this program. In the noncardiac field several new operative technics as well as concepts deserve mention.

Portal hypertension, whether extrahepatic or intrahepatic, with its associated ascites, esophageal varices and the threat of death from hemorrhage, has always stimulated surgeons. Rienhoff (3) in 1951 reported for the first time simultaneous ligation of the splenic and hepatic arteries in 6 cirrhotic patients, who apparently improved following the operation. This thesis has been widely tested and certain facts seem to emerge (4). The ability of the cirrhotic liver to withstand occlusion of its major arterial supply has been demonstrated. The concomitant use of a large amount of antibiotics, which was thought to be a prerequisite for operation, is probably not as important in the human as in the dog, since the dog apparently has a contaminated liver under normal circumstances. However, the long-range effect of this procedure on portal pressure has been disappointing, since the hypertension usually returns within a few months (5). Crile (6) has reported satisfaction with an esophageal "hemorrhoidectomy" (excision of the varices) performed through the open esophagus. This approach is appealing, because of its simplicity and direct attack at the point of maximum danger. Porto-caval and spleno-renal shunts are operations of such magnitude as to be almost contra-indicated in the type of patient for whom they are designed. A recent aid in the diagnosis of portal-vein obstruction is the venogram, obtained by injecting a contrast medium (Diodrast) into the spleen; it serves to differentiate intra-hepatic from extrahepatic portal obstruction (7). Insufficient time has elapsed for appraisal of this method.

A recent advance of real value has occurred in the management of peripheral vascular disease, namely, an increased awareness of the inherent advantages of lumbar sympathectomy. The response of the peripheral vessels to spinal anesthesia was formerly considered helpful in selecting those patients who would benefit from excision of the lumbar sympathetic chain. This is erroneous, and if this test is used it will deny many patients the benefit they would have received from operation. Lumbar sympathectomy is of great value in Buerger's disease, in causalgia, in arteriosclerotic ischemia, and in the chronic indurated leg with ulceration, whether from phlebitis or from varicose veins. We recently obtained an excellent result following sympathectomy in a 14-year-old boy with recurrent ulceration in an old burn scar and associated vasospasm. Pratt (8), who has done much to demonstrate the effectiveness of sympathectomy, recently reported an amputation incidence of 3 per cent in patients with peripheral gangrene—truly a remarkable achievement.

Among the controversial points in surgery, the relative roles of subtotal gastrectomy and vagotomy in the surgical treatment of peptic ulcer seem to be well delineated at present. Only a few surgeons today prefer vagotomy as the primary surgical procedure; subtotal gastrectomy seems thoroughly established as choice of the majority. Vagotomy is reserved for those patients who have recurrent ulceration after an adequate gastrectomy.

The recent development by Henry Bahnson (9) at Johns Hopkins Hospital of a standardized operative technique for aortic saccular aneurysms seems to hold considerable promise. By using a curved Pott's multitoothed clamp, he divides the neck of the sac and closes the aortic defect, thus maintaining aortic continuity; the sac is then excised. Aortography has drawn much attention recently

and various techniques are in use. The disadvantages of translumbar installation of contrast medium into the aorta have led to the development of percutaneous transfemoral aortography. In this method, the femoral artery (under local anesthesia) is cannulated with a 15-gauge needle through which a long flexible stylet is inserted. The needle is then withdrawn, a plastic tube is inserted over the stylet to the desired level, and the contrast medium is injected.

Fortunately the inadvertent division of both recurrent laryngeal nerves during thyroidectomy is becoming a rarity, as operative techniques improve. This decreased incidence could be classified as a fairly recent advance in surgery. However, the occasional patient with this distressing complication presents a problem which has not yet been completely solved. The glottis must be widened sufficiently to allow an airway and yet not enough to eliminate phonation. For over two years the authors have followed 2 patients in whom a completely new operative procedure was carried out. A stent of heavy stainless-steel wire screen was inserted into the opened larynx in order to separate permanently the anterior commissure. It is an easy operation and has produced excellent results in both patients. Perfect healing over the exposed screen has occurred, although it was necessary to remove excess granulation tissue on one occasion from each. Both patients are decannulated and have satisfactory voices.

Tracheotomy as a therapeutic procedure should be mentioned. Its value is being rapidly recognized in the management of the acutely ill patient following chest trauma, head injuries, severe burns, tracheobronchitis, or extensive thoracic or thoraco-abdominal surgery. The benefits of tracheotomy are obvious; the dead space is markedly decreased, secretions are readily aspirated and, in the comatose patient, tracheotomy may avert disaster. Spontaneous closure occurs rapidly after removal of the tube.

We consider the development of stainless-steel wire screen for surgical purposes to be of great benefit in occasional highly selected cases. In addition to its use in laryngeal palsy, we have found it to be helpful in the following conditions:

A. Hernia
   - Inguinal
   - Incisural
   - Diaphragmatic

B. Facial paralysis
C. Maxillo-facial restoration
D. Skull defects

Total gastrectomy for carcinoma is becoming a more common procedure but generally leaves the patient in such an unenviable state of malnutrition that the potential value of the operation in the cure of gastric cancer is not being realized. In this regard new methods of restoring the gastric pouch have been proposed. One such technique utilizes the right colon and terminal ileum interposed in an isoperistaltic fashion between the esophagus and the duodenum. Another uses the mid-portion of the transverse colon as an antiperistaltic stomach. Isolated and reduplicated loops of jejunum are used in a similar manner. It is probably safe to predict that when a wholly satisfactory technique for gastric replacement is

available, total gastrectomy will become the operation of choice for gastric carcinoma.

As the field of surgical endeavor widens, much credit should be given to the medical anesthesiologists for the major role they have played in this advance. Their counsel in the choice of the anesthetic agent, their aid in the preoperative evaluation, and their management of the anesthetized patient have added a great deal to the safety of the operative procedure and have been instrumental in extending surgical boundaries to their near-ultimate limits. The relationship between surgeon and anesthesiologist, to be most productive, should be one of cooperation and mutual respect.

MORE PROMPT AND COMPLETE REHABILITATION

Immobilization of the patient has many undesirable and adverse effects. It is important therefore not to compound the hazards of surgery with the disadvantages of immobilization. Early ambulation, within reason, is now accepted almost without reservation as being of unquestionable benefit, in many ways. Pulmonary complications are reduced (aided no doubt by antibiotic therapy), protein metabolism and wound healing are aided, and peristalsis is stimulated. Probably most important of all is the improvement in the general attitude of the patients, because they feel they are progressing and that the "crisis" is past.

Another concept which has been greatly modified is the role of surgery in the afflictions of the aged. It has been clearly shown that the risk of surgery is not materially increased by age alone, if *elective* procedures are considered. The laissez-faire attitude toward lesions of the aged, such as hernias, gall-stones and colonic cancer, simply leads to the increased risk and high mortality of *emergency* surgery when the patients are slightly older and in much poorer condition.

John D. Stewart (10) has stated this concept admirably in his comments on The Deacon's Masterpiece:

> "Have you ever heard of the one-hoss-shay,
> That was built in such a logical way
> It ran a hundred years to the day."

The same approach to surgical lesions of the aged as to those of middle-age will change the well-worn phrase "too old to be operated on" to "too old not to be operated on." Thus our oldsters, like the Deacon's masterpiece, can go "all to pieces all at once." "All at once and nothing first,—just as bubbles do when they burst."

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FROSTBITE THERAPY*

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INTRODUCTION

The problem of exposure to cold and moisture exists in civilian as well as in military life. A disaster caused by a cyclone or flood may remove the protection of warmth and dryness, forcing many to an exposure for which they are unprepared. A man's work may require him to go in and out of a refrigerator car or a deep-freeze. The repair of a damaged water or sewer main or a dike during winter in any modern city exposes the workman to dampness and cold (1). The increase of longevity to an average age of 77 is associated with an increase in the number of persons of advanced age in out-of-door jobs despite their physical inadequacies. Such people with diseased vascular systems are likely to damage their extremities severely by exposure to even mildly cold temperatures. In a controlled study, we found 40 per cent of male workers and 19 per cent of female workers over the age of 40 had some degree of arteriosclerosis. Such a group is particularly susceptible to the effects of cold (2).

Frostbite in the Armed Forces

The Korean war has brought home the military importance of frostbite even in these modern times. The First Marine Division was cut off by an unexpected invasion of Chinese Reds near the Chang Jin reservoir. They fought their way back from the Yalu River for two weeks through freezing temperatures, exposed not only to the rigors of winter in that country, but also to a stalking enemy who was watching for a weakening in the resistance of our forces. Figures 1–3 show typical frostbite casualties.

The Romans first reported the military importance of frostbite while fighting in the mountains. The loss of heart of the Grande Armée in the Moscow retreat, due to exposure and subsequent frostbite, doubtless led to the eventual fall of Napoleon's army at Waterloo. Some countries, such as Switzerland, have been singularly free from invasion because of the hardships from cold confronting the invaders in the icy mountains.

Powerful armies have been completely immobilized by this situation. In World War I, trenches filled with a few feet of water exposed many men to cold, moisture and trauma. It was found in 1916 and 1917 that successful progress could be made with small expeditions well equipped with warm, dry gear. One

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A B

FIG. 1. **A**. Gangrene following frostbite. Exposure complicated by trauma. **B**. After demarcation and self-amputation. Subsequent therapeutic plastic graft. (Courtesy of U. S. Naval Hospital, St. Alban's, Long Island, N. Y.)

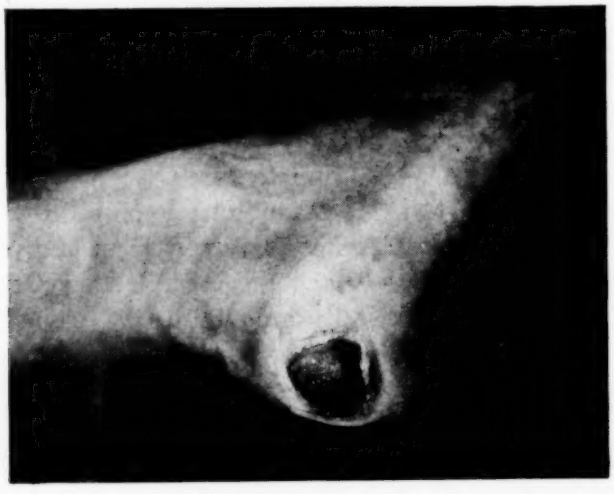

FIG. 2. Gangrene of heel. Frostbite exposure, and trauma of pressure on heel. Patient sat in weapons carrier and pounded heel "because it was numb." (Courtesy of U. S. Naval Hospital, St. Alban's, Long Island, N. Y.)

noted general believed that the first World War would have been won sooner had these small but well trained troops been used more expeditiously on the coldest days—the days when the enemy was busy fighting exposure.

On the Aleutian Islands (in Attu) in World War II, the freezing temperatures were nearly a deciding factor in this campaign. Wet, exposed to the weather, and unable to make a shelter on that forsaken island, the American soldiers were pinned down on the shore immediately by well concealed troops. The amputation rate in this group was high (26 per cent). The Japanese who survived suffered an even higher amputation rate (70 per cent), due to poorer hygienic conditions.

FIG. 3. Frostbite. Partial loss of toes. (Courtesy of U. S. Naval Hospital, St. Alban's, Long Island, N. Y.)

The captured diary of Herman Goebbels provides further evidence of this military problem:

(Transl.) March 6, 1942. Our losses in the East for the period of June 22, 1941 to February 20, 1942 were 199,448 dead (including 7,879 officers), 708,351 wounded (including 20,992 officers), 44,342 missing (including 701 officers)—a total of 952,141 (including 29,572 officers). Until February 20, 112,527 cases (more than 12 divisions) of freezing or frostbite were reported." (3).

That gunfire and shells could not win the victory over cold was illustrated in the Battle of the Bulge where whole German divisions were prevented by the cold casualties from a breakthrough at an advantageous time. This common enemy could easily be the victor over both sides. In the 8th Air Force, the casualties from frostbite exceeded those from gunfire in the period from August 1942 to January 1944. Similarly, of the first 70,000 casualties reported in Korea, one-half were due to exposure to cold. When one considers the possibilities of another great war being fought, probably in the Arctic, one realizes the importance of this problem, in military as well as in civilian life.

Other problems of cold

With exposure to cold, the temperature of the central portion of the body seldom goes below the rectal temperature of 37 degrees Centrigrade (4). The temperature may fall below this critical point, however, in the superficial and peripheral areas, due either to local cold trauma such as direct contact with ice, or to general exposure. Wind increases the tendency to traumatic lesions, and frostbite has occurred within the range of 8 to 14 degrees Fahrenheit (minus 13 to minus 10 degrees Centigrade) in areas struck by a strong wind. Some people are able to withstand temperatures as low as minus 20 degrees Centigrade without evidence of freezing. Physical surroundings (such as humidity and wind) and the patient's general physical condition, age and ability to resist cold are

major factors in the incidence of frostbite. The part which physical status plays has been shown in experiments on rats. Rats weighing under 19 grams died before their tails were frozen at a temperature of 10 degrees Centigrade, whereas those weighing over 25 grams survived (5, 6, 7).

Immersion foot. The alarming toll of sunken ships in the last war exposed many men to cold and wet. In the forced run to Murmansk, Russia, against determined resistance, with supplies the Russians used against Hitler's men at Stalingrad, often up to 50 per cent of the convoys were destroyed. The starved survivors drifted for days in freezing waters in open lifeboats, their feet wet, dependent, and swollen. On the basis of much experience, these seamen were treated in hospitals by ultraconservative methods, both in Europe and on this continent. Trauma was minimal in this group, because they sat in boats; consequently the amputation rate was low. "Immersion foot" became the descriptive term for this condition. The symptoms were caused by hypoproteinemia, starvation, wetness and dependency, in addition to cold. "Immersion foot" is the nautical mate of "trench foot."

Over 60 per cent of the Marines with severe frostbite had antecedent wet feet. When a limb is wet the possibilities of freezing are greatly enhanced, due to better conductivity. Likewise, if trauma occurs, the incidence of tissue loss increases. The term "trench foot" indicates a serious exposure to cold complicated by the trauma of standing, walking, or other injuries to the feet.

Movement of the part reduces the loss of tissue. Gangrene of the heel was prevalent in those Marines who, because of their injuries, had to ride away from the ambush in Korea in vehicles. They could move their toes and thus forestall freezing of this part of the foot, but freezing of the heel resulted because there was pressure in that area, in addition to the cold. This effect of local trauma is well illustrated in Figure 2. Exhaustion and inactivity add to the incidence, as do concomitant injuries.

SYMPTOMS OF FROSTBITE

There may be no forewarning symptoms of frostbite (50 per cent of the Marines who suffered casualties were unaware of the time when their lesions developed.) Usually, the first symptom is a painful burning sensation, followed by cold and numbness. Larrey (8), Napoleon's chief surgeon, accurately described this feeling, "as if the feet are made of wood." (3). In discussions with the Marine patients, it was found that there was a relative frequency of early numbness. Many of these men pounded their rifle butts on their feet, hoping to secure feeling and to get the "circulation started again." Thus, trauma was added to an already serious vascular problem.

Often, the exposed men removed their boots in their efforts to obtain relief. Later it was impossible to replace the shoes because of the swelling. One hundred and fifty years ago, Larrey counteracted this possibility in the French army by issuing an order that no man could remove his boots. The temperature, the duration of the cold injury, and the medium in which the patient had the exposure (*e.g.*, water or air) are related to the symptoms.

Exposure to cold in high-altitude flying is accompanied by anoxemia and this increases the tissue destruction. The symptoms under such conditions begin with anoxemia, followed by blanching and vesicle formation. At first there is some bluish discoloration, due to venous congestion and some edema. As the condition continues, the part becomes white, pale and cold; later, the part may become marble white. In other cases, rapid necrosis and gangrene may occur.

A modification of the classification of cold injuries by degree, as made by Wright and Allen (9) in 1943, follows:

1. *First degree frostbite* occurs in patients who have been subjected to cold for a short period of time, or to a minor degree of cold for a long time. The symptoms are erythema and spasm, with a burning, tingling sensation. Some peeling of the skin may result, but these patients have no permanent loss of tissue.

2. *Second degree frostbite.* In this phase there are symptoms of anesthesia and paresthesia with a marked reactive hyperemia; often wheals and superficial blebs occur. There is actual tissue destruction, but this is usually limited to the skin. Secondary infection or trauma may increase the tissue loss.

3. *Third degree frostbite* is due to extreme cold. There is damage to the subcutaneous tissues, with incomplete recovery. If a large part of the body is exposed and the effects are continued for a long time, death results. The amount of tissue loss depends also upon the severity of trauma and secondary infection. This degree of frostbite is directly influenced by the type and effectiveness of the therapy.

4. *Fourth degree frostbite* results in the loss of major tissues such as muscles and bones.

5. *Fifth degree frostbite.* Anoxemia and cold associated with high-altitude flying is the cause of this cold injury. Although basically a military problem, civilians may be exposed in the course of commercial airline flights in the stratosphere in pressurized cabins. The symptoms are a shiny and tense skin area, with subcutaneous hemorrhages. Such exposure may be likened to that in a deep-freeze ice box. Cellular death occurs early.

PATHOGENESIS OF COLD INJURY

It is difficult to simulate in the experimental animal the conditions under which frostbite develops in man. However, the pathology and pathogenesis of the changes after exposure to cold have been studied. It is found that the pathology varies with the length and degree of exposure, the associated factors such as moisture and wind, other injuries, and the age and resistance of the patient. Results of investigations of the tissue alterations and the reactions to various types of therapy have been contradictory, and therefore these changes are not clearly determined.

The supposition has been for years that the changes after cold injury were due to the direct effect of cold on tissue cells, similar to the effect of heat in burns. Another theory was that tissue injury was secondary to a vascular lesion, *i.e.*, vasodilatation, vasoconstriction, sludging of blood cells, and thrombosis. According to the first theory, the vascular changes following frostbite are secondary.

We have found in our own observations that the vascular changes are important. The true pathogenesis is probably cell damage combined with the vascular changes.

A major factor in the determination of recovery is the amount of vascular occlusion, even though it may not be the initial lesion. We have noted a surprising number of recoveries in many frostbitten limbs when it appeared that the tissue cells had been destroyed. Such recovery must be due to the fact that the circulation to the part had not been irreparably damaged.

The pathology is undoubtedly *both* an injury to the tissue cell and a local ischemia which is caused by clotting in the peripheral vessels. This change is greatest at the capillary level. The retardation of the venous flow is due to the erythema which first occurs when the part becomes cold, combined with damage to the capillary bed. The bleb formation perhaps is due to the stasis of lymph caused by the failure of the circulation to remove the tissue fluids.

In the presence of gangrene of a cyanotic avascular type, a black, dry, "sock or glove-like" necrosis develops. Often these black skin "molds" will shed, revealing a healed or a healing area. Secondary infection will alter the prognostic and prophylactic picture. As in burns, there is no standard pathologic description. Many factors have to be considered in analyzing the degree of destruction.

TREATMENT

Prophylactic Therapy

In civilian life, the prevention of frostbite is of most importance. Elderly patients, and those with arteriosclerosis or diabetes must be protected from *out-of-doors work* in cold and wet weather. The clothing must be sufficient and those who work in refrigerated rooms or wet areas must be observed carefully for cold injuries. The patient who is hurt out of doors is especially susceptible. *Wind breaks* should be provided and care of the parts carefully observed.

In military life, *discipline* and its enforcement prevent frostbite. The value of *hygiene*, cleanliness and the use of additional dry socks and shoes should constantly be stressed to these men. An example of the effect of carelessness on the incidence of cold injuries was shown in the Air Force during the Battle of the Bulge in World War II, when 500 men were evacuated each week because of high-altitude frostbite. One out of 10 of these men was a pilot who before trauma cost this country $50,000 in addition to the months of time for training. The frostbite was due most often to faults in electrical clothing caused by their careless handling thereof. It was an automatic court martial offense in one allied Air Force to misuse such protective equipment. This order resulted in an immediate decrease in the incidence of frostbite due to high-altitude flying.

The major precautionary measures in frostbite prevention are as follows:

a. *Wearing apparel.* Careful attention should be given to proper clothing, footwear and other covering, if one is to be in freezing temperatures. Water-tight equipment should be ideal. It was tried but proved to be impractical and dangerous, for it does not permit the evaporation of perspiration which, as it becomes

cold, freezes and increases the pressure on the skin. Thus, water-tight boots are not safe unless they permit evaporation.

b. *Dry apparel.* It is important that shoes and socks be kept dry. Military life has provided ingenious devices for drying gear, *e.g.*, "canned heat," exhaust fumes, or flashlight-battery heaters. Electric dryers woven in clothing will be the ultimate answer.

c. *Motion.* Movement of the parts is also a preventative measure against cold injury. Men who are exposed to freezing temperatures should be kept moving about constantly and no one should be allowed to sleep, unless in a protected and warm area.

d. *Cleanliness and the prevention of infection.* If the part is not clean, and a break occurs in the skin, infection will result and there will be an increase in the amount of tissue loss. Therefore, it is most important to avoid infection by insisting that men in the Services take baths and change all wearing apparel before being subjected to cold conditions. This situation must be explained to the men, for the reasons often are not understood fully and the orders meet with opposition. These measures apply also in civilian life. The use of antibiotic therapy will aid prophylactically in those who who may be exposed.

Active Therapy

It is important that the treatment of lesions caused by frostbite be started immediately. The exposure to cold or moisture must stop. Care should be exercised in attending to the removal of any constricting garments, such as tight bandages or clothing. Patients who have been slightly exposed will need only hygienic care. When there is destruction of tissue, the patient should be placed at complete bedrest, as the bearing of weight upon limbs with open injuries will result in an increase in tissue loss and morbidity. The wounds should be classified as to the degree of frostbite and, if possible, treatment should be carried out according to these categories:

General measures

In patients who are in a state of shock, *stimulants* may be required. Whiskey has been found to be an excellent drug for this condition, due to its general and vasodilating action.

Antibiotic therapy

Antibiotic therapy should be started in the treatment of all such patients. Specimens from the open wound should be taken for culture; any organism found should be tested for sensitivity to the drugs. Until the reports regarding the proper drug to be used are available, penicillin may be administered empirically.

Complete abstinence from smoking

This is of great importance. Even a small amount of nicotine produces marked vasoconstriction. Many limbs have been lost unnecessarily because nicotine-induced vasoconstriction interfered with the collateral blood supply in patients

with occlusive arterial lesions. All frostbitten patients are in the same category when first treated.

Local treatment

Local cleansing may be performed with one of the sulfonated detergents (*e.g.*, pHisoHex) to which hexachlorophene has been added. This cleansing must be atraumatic and care should be used to prevent any tissue injury or break. Sterile dressings should be applied to any open wounds, unless they are not infected. In that case the wounds may be left exposed on a sterile sheet, and the bed clothing kept from them by a cradle or bed cage.

In the past, the loss of limb and life was extensive when the cold exposure was treated by rapidly warming the part. Blebs formed and a rapid rate of tissue destruction and gangrene followed. In World War II the part was brought back to normal temperature gradually over a period of many weeks. Investigation has been undertaken to determine the environmental temperature which results in the least tissue destruction. These studies have been made possible by the large number of cold casualties during World War II and by the new ones from Korea. Direct inference from experiments on animals is impossible, owing to the species difference in circulatory systems. It is also impossible to simulate in the laboratory animals, the fatigue, trauma, wetting and variable temperatures that the Korean veterans underwent.

In experimental animals there is evidence of injury to the tissue cells in extreme cold, similar to that due to a burn. The vascular changes, such as sludging, thrombosis and clotting then occur secondarily to the cell injuries. On the basis of these tests on animals, some investigators have advocated a rapid restoration of the cells to normal conditions and temperature in order to lessen the subsequent necrosis. The vascular problem, however, is a major one and the vascular condition contributes considerably to tissue destruction or to the actual loss of the extremity. It may not be the primary problem in patients exposed to intense cold, but the tissue necrosis secondary to thrombosis determines the final outcome in the affected part.

There are two methods for treating frostbite, namely, by slow warming or by rapid warming.

Slow warming. Slow warming was adopted because of the poor results obtained in the past with rapid warming. World War II frostbite victims were found to have less gangrene if the part was kept cool. The optimal temperature is believed to be between 55° and 60° Fahrenheit. The greatest damage to a frostbitten area occurs in the venous and lymphatic vessels, associated with stasis, bleb formation and edema. Theoretically the cooling prevents the delivery by the arteries of more blood to the part than the veins and lymphatic vessels can remove from it.

This method is relatively simple. The use of a bed tent under which ice bags are placed, and the application of electric fans aid in keeping the temperature at the optimal level. Pain disappears when the part is kept cool. During the last war, before cooling therapy was employed, the patients often were found at an open window with the injured part placed outside. This type of treatment should

be continued for from three to five weeks, or until the fate of the part has been decided.

Rapid warming. Many investigators (5, 6, 7, 10, 11, 12) have experimented with rapid warming as a method for quick restoration of the affected part to room temperature. They found, in animals, that if the part was warmed but not heated there would be no greater, and often less tissue loss. Lewis (13) discovered evidence of muscle degeneration fifteen to thirty minutes after local cold injury, and found that under similar conditions the muscles of a rabbit's legs made ischemic by a tourniquet showed no muscle degeneration.

The part that blood-cell sludge plays is unknown (14, 15). Sludging does follow injuries and may be of paramount importance in the development of gangrene. With even a short exposure, the possibility of permanently injuring the muscle cells exists. If this is so, it is difficult to understand why certain organisms can be kept under refrigeration for a long period of time without injury, why animals can hibernate without injury, and why the preservation of certain tissues by the deep-freeze method does not destroy them. Such preserved tissues have been used successfully at later dates for graft purposes. Cold therapy for cancer pain does not cause tissue destruction. The reason for the absence of large blebs and edema when the part is rapidly warmed, has not been clarified as yet.

Despite the questions which rapid warming poses, the animal experiments cannot be discounted. It has been shown recently (6, 7) that the rapid warming method causes less loss of tissue than the slower cooling method. These experiments were performed on animals in which the effects of human frostbite were simulated by slowly freezing their parts. Rapid warming therefore is the treatment of choice.

Antithrombotic therapy

The early use of antithrombotic drugs is advocated for frostbite, if the nature of other wounds does not preclude their use. Encouraging results have been reported (16–19).

Heparin should be started at once in conjunction with one of the other oral antithrombotic drugs. The oral drug should be used at least three weeks or until the fate of the part has been determined. We have used Tromexan (ethyl biscoumacetate) in our patients with good results (18–22).

The following program has been used:

Selection of patients. The dosage of these drugs must be modified for the aged, for those with other diseases, and for those with an abnormal response. It must be individualized for each patient and controlled with consistently accurate laboratory tests. The outlined program applies to those who do not have other hemorrhagic injuries and who have normal liver, heart and kidney functions.

Dosage. Heparin is administered during the first twenty-four hours. A dose of 50 mg. is given intravenously, and 30–70 mg. by deep subcutaneous injection. Two hours after administration, the coagulation time is tested. Then 30–90 mg. of heparin is injected subcutaneously every four hours, to maintain the coagulation time between twenty and thirty minutes. One of the oral antithrom-

botic drugs, Tromexan (1,200 mg.) or Dicumarol (300 mg.), is administered jointly with the heparin.

As soon as there is evidence of a prolonged prothrombin time, the heparin is discontinued; when Tromexan is used, this can be after a period of twenty-four hours. Additional doses of the oral antithrombotic drug are administered daily, depending upon the prothrombin time. The maintenance dose of Tromexan is 600 to 900 mg. and of Dicumarol, 50 to 150 mg. The prothrombin time is maintained at two or three times the normal control level.

Antithrombotic therapy should be continued for a minimum of three weeks, or until such time as the outcome is no longer in doubt.

If hemorrhagic complications develop, they must be recognized and treated immediately. If it is necessary to reverse the antithrombotic tendency because of operation, a draining wound or other complications, this may be achieved by the use of blood transfusions and of specific drugs such as Protamine instead of heparin and vitamin K_1 instead of Tromexan or Dicumarol.

Additional measures

Antibiotic drug therapy should be started at once. Wound culture and the sensitivity test will determine which drug to use. This therapy must be combined. Antihistaminic drugs, such as Benadryl, particularly in combination with rutin, have increased the salvage rate of severely frozen limbs experimentally.

Pressure dressings, such as plaster casts or other support may cause damage, especially if edema is present. They may also conceal infection. Mild support for the prevention of bleb edema is advised.

ACTH and cortisone have had no effect on the results. Mephenesin (Oranixon), which relieves spasm of smooth muscle, is of great help in the control of pain in these patients, and many of them preferred it to opiates.

Surgical therapy

The most important surgical approach in treating these patients is surgical restraint. An extremity should not be amputated unless there is actual evidence of a spreading infection which jeopardizes the patient's life. The appearance of a black toe or "ulcers" often is the signal for an over-ambitious or untrained surgeon to amputate. Restraint, therefore, must be emphasized. The black coloring often is only skin deep, and is likely to shed like a snake's skin with time, revealing a granulating viable tissue.

During the recent Korean campaign, a series of 182 patients was treated in one of the large Naval hospitals on the East coast and only 4 required a major amputation, an incidence of 2.2 per cent. These figures are consistent with other reports during this period (23).

Surgical restraint does not mean ignoring the draining of a fluctuant suppurative process. The surgical indications for this procedure are definite. At times, major amputations are required, as in the patient with gas gangrene and other uncontrollable infections; but these amputations become less frequent as the surgeon practices conservatism. An operation should not be performed

for the gangrene of frostbite but only for a spreading uncontrollable infection, which is almost unknown with the modern use of antibiotics.

Intermediate treatment. In the patient with a cold injury, the period from the second to the twelfth week is of great importance. The part may be kept clean by soaks or whirlpool baths with one of the sulfonated detergent soaps, *e.g.*, pHisoHex. This helps in the separation of dead tissue. The part also should be exposed to the air. Weight bearing on the extremity is contraindicated until the wound is healed or separation has occurred. At this time, sterile dressings should be applied. Antithrombotic and antibiotic therapy should be continued.

If there is evidence of a deficient arterial supply to the part, sympathetic nerve interruption may be of value in *selected* cases. The response to a nerve block may indicate whether or not sympathectomy will be successful. A chemical agent such as Priscoline or tetraethylammonium chloride, or one of the intravenous anesthetic agents, may be used for the nerve block. In some patients, the results of sympathectomy are equivocal, but in those in whom sympathetic block improves the local lesion, surgical interruption reduces the loss of tissue.

Hyperhidrosis is a complication in these patients. If it does not respond to hygienic and conservative measures, surgical sympathectomy is of great value.

Causalgia is another complication. The foot becomes red, shiny, and extremely sensitive, in association with parasthesias. This condition also can be relieved by surgical sympathectomy.

Amputation or graft. After the separation is complete, one must then decide on whether amputation, or a plastic graft is indicated. Any part of the patient's limb on which he can stand and bear weight is better functionally than the best prosthesis; hence the great importance of saving as much of the limb as possible. Sufficient time should be allowed for separation of diseased tissue from the living part before anything as irrevocable as an amputation is contemplated. Skin grafting may save many partially lost limbs.

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STEREOENCEPHALOTOMY IN THE TREATMENT OF PARKINSONIAN TREMOR*

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In a considerable number of cases the tremor of Parkinson's disease is not relieved by medication. In such instances, three types of operations are performed at the present time: extirpation of the precentral cortex (Bucy (1)), removal of the caudate nucleus and section of the anterior limb of the internal capsule (Meyers (2), Browder and Rabiner (3)), or incision into the lateral column of the spinal cord (Putnam (4)). These operations unfortunately impair voluntary movements to a significant degree. We attempted, therefore, to devise a procedure that would be relatively safe and would relieve the tremor without interfering with important functions such as volitional movements.

Whereas unilateral interruption of the afferent impulses in the midbrain is ineffective in significantly diminishing the tremor, and thalamotomy has at the most only a slight effect for a few days, a definite reduction of the tremor can be obtained by the production of lesions in the ansa lenticularis (ansotomy) (Wycis and Spiegel (5)). In Russell Meyer's procedure, in order to interrupt pallidofugal fibers the third ventricle is entered and its lateral wall is incised. This author reports a favorable effect upon the tremor, but considers the risks of this operation too great to warrant its general employment in the treatment.

METHOD

Since we have had some experience with stereoencephalotomy in operations on the basal ganglia in patients with choreic movements, we applied a similar technique for interrupting the ansa lenticularis (ansotomy) in the treatment of the tremor of paralysis agitans. In order to spare the fibers of the internal capsule as much as possible, our stylet electrode was inserted through the frontal lobe in an anterodorsal-ventrocaudal direction, so that its tip reached the base of the globus pallidus approximately at a point corresponding to the ventral end of the internal medullary lamina or a few millimeters laterally. Lesions were made in medial and posterolateral directions.

RESULTS

Up to the present time we have had the opportunity to apply this method in 6 cases of typical parkinsonian tremor which had not been improved by routine medical treatment. Following ansotomy, the tremor on the side opposite

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the ansotomy ceased almost completely in 2 cases (Case I, tremor of ten years' duration; Case IV, tremor of three years' duration). At present, there persists only a slight tremor of the thumb in one of these patients (Case I); and only under emotional excitement can there be noticed a slight shaking of the hand in either patient. The improvement has been maintained in these 2 cases for the duration of observation—nine months and three months, respectively. Some diminution in the amplitude and frequency of the tremor of the hands was observed in another patient (Case III) who had postencephalitic parkinsonism of seven years' duration. This improvement has been maintained to date for six months on the left and three months on the right side. The tremors of the lower extremities, fixed facial expression, bent-over attitude, and propulsive gait were not altered in this patient. In 2 patients (Case II, very advanced postencephalitic parkinsonism of over twenty years' duration; and Case V, left-sided parkinsonism of one year's duration) the effect on the tremor was only transitory (about four and two weeks, respectively). In the sixth case (right-sided parkinsonism of seven years' duration) the coarse tremor was changed into one of very small amplitude. In this instance, however, the follow-up period (two weeks) was too short to arrive at a definite conclusion.

Electromyographic studies showed that the typical rhythmic discharges either ceased completely for long periods or were markedly diminished in amplitude. Sometimes there was also a slowing of their frequency (*e.g.*, from 4.6/sec. to 4.0/sec.). In some cases the rhythmic discharges were still present, although no tremor was visible on inspection. Of particular interest was the disappearance or reduction of the rhythmic discharges in some muscle groups, *e.g.*, the extensors of the forearm, although such discharges were still present in the antagonists. Contrary to expectations, ansotomy failed to increase the muscle tone. In some instances, there was even some reduction of the resistance to passive movements and of the cogwheel phenomenon (in Case III, in the flexors of the hand).

The voluntary movements were preserved in all cases, and there were neither pyramidal-tract signs (Hoffman or Babinski) nor increases of the tendon reflexes on the affected side. Occasionally a slight temporary reduction of the motor power was noted. However, it should be emphasized that, with the return of motor power, the tremor did not reappear. The ability to perform alternating movements in quick succession was not impaired, and in Cases III, IV and VI it was even improved. In Case III this was associated with a reduction of muscle tone, but in Cases IV and VI the increase in frequency of alternating movements developed without changes of muscle tone. There was no impairment of sensation.

When the electroencephalogram, the electropallidogram and the electromyograms of the affected muscles were recorded simultaneously under local anesthesia just before ansotomy, it was found that the pattern of rhythmic bursts for the affected muscles was not accompanied by corresponding fluctuations in the pattern for the cortex or pallidum. Such records further show that distinct regular electrical discharges, at frequencies comparable to the cortical alpha and beta rhythms, may be led off from the pallidum.

DISCUSSION

The foregoing observations indicate that severe impairment of the pallidum is hardly a prerequisite for the development of parkinsonian tremor, and that the tremor-genetic area must be sought in lower levels. Since the substantia nigra usually shows a severe degeneration in paralysis agitans and since stimulation of the mesencephalic and pontine tegmentum may induce tremor in cats (Spiegel, Kletzkin and Szekely (6), Folkerts and Spiegel (7)), it may perhaps be assumed, as a working hypothesis, that parkinsonian tremor is due to a release of the reticulate substance of the tegmentum from nigral inhibition. This would also explain the observation of tremor following lesions of the ventral part of the tegmentum in monkeys (Ward *et al.* (8)).

Within the framework of our concept, the beneficial effects of ansotomy in paralysis agitans may be explained by assuming that the globus pallidus sends facilitating impulses to the tremor-genetic center in the mesencephalic or pontine tegmentum and that interruption of pallidofugal impulses by ansotomy removes this facilitating effect[1].

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[1] Following the presentation of this paper at the meeting of the American Therapeutic Society, Cooper reported before the American Neurological Association, Atlantic City, June 15, 1953, that he was able to obtain alleviation of involuntary movements and of Parkinsonian tremor by ligation of the anterior choroidal artery. His interpretation that the success of his operation is due to elimination of the pallidum is in agreement with our concept regarding the role of the globus pallidus in the genesis of choreatic movements (9) and of tremor, and with our operative results following the production of stereotactic lesions of the pallidum in chorea (10) and in the ansa lenticularis in Parkinsonian tremor (5). However, ligation of the anterior choroid artery seems to be technically more difficult and more hazardous than ansotomy. The latter procedure interrupts a well-defined system, whereas the area supplied by the anterior choroid artery is somewhat inconstant. As pointed out by Cooper, it may include besides the globus pallidus and the ansa lenticularis, the red nucleus, the retrolenticular portion of the internal capsule, the corpus Luysii, the substantia nigra, the optic tract and the cerebral peduncle. Interference with the functions of these latter structures would induce rather undesirable side-effects.

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THE USE OF TRACHEOTOMY IN THE CRITICALLY ILL PATIENT*

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In early 1949 the routine use of tracheotomy for acute chest injuries was instituted at the Ancker Hospital, St. Paul, Minnesota (1). This procedure was introduced in order to obviate the necessity for repeated bronchoscopic aspirations when bronchial secretions are profuse. Patients in a state of coma or in a greatly weakened condition are unable to bring up these secretions and subsequently may die of bronchopenumonia. We have used tracheotomy since 1949 in patients with various conditions other than thoracic injuries (2). Creech, Woodhall and Ochsner (3) have reported on the importance of tracheotomy in the treatment of pulmonary complications associated with tetanus. We do not take the view that bronchial secretions should be tolerated in critically ill or unconscious patients and that patients should come to autopsy with "terminal pneumonia." For too long tracheotomy has been considered a procedure to be used only for an acutely obstructed airway. It should have a place in the equipment of the surgeon and internist for the purpose of combatting the complications which often hasten death.

Recent textbooks and even articles describe the ease with which a nurse can pass a nasal catheter into the larynx and obtain adequate suction in the tracheal and bronchial passages of an unconscious patient. This undoubtedly is true of the experienced nurse, trained in the fine art of postoperative care; however, the usual general duty nurse is either reluctant to insert the catheter into the larynx, or has not had the experience necessary to know when the trachea has been cleansed properly. In the case of the unconscious or critically ill patient, we have found it necessary to rely on a bronchoscopist in order to gain adequate suction by this procedure, which should be carried out as often as every thirty minutes for adequate cleansing of the respiratory tract. However, as is well known, repeated bronchoscopic aspirations are attended with much laryngeal trauma and bleeding. Tracheotomy would therefore offer a more efficient route and would bypass an organ which should be carefully guarded. When a catheter is inserted through a tracheotomy tube, the cough reflex is maintained, even in the most profound stupor. The additional help of the suction catheter in removing the sputum when it is raised saves the patient considerable strength, since it is only with great effort that he can expel this sputum through the larynx. The larynx is an efficient block to both air and sputum in an unconscious patient.

In addition to acting as a passageway for a suction catheter, tracheotomy reduces the volume of tracheal dead space and removes the resistance of the

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vocal cords to air exchange. Thus Carter and Giuseffi (4) found that by means of tracheotomy the dead space in the respiratory tract was reduced from roughly 150 cc. to 50 cc. This made 100 cc. available to the alveoli of the lung for ventilation, an amount which in some instances may be very significant.

RESULTS

As mentioned earlier, tracheotomy has been used at the Ancker Hospital for a variety of conditions. Though many of the patients were critically ill, in other instances our past experience led us to institute tracheotomy before the stage was reached when a rapidly developing respiratory problem was inevitable. The procedure we used need not be discussed here, as it is fully described in any textbook of surgery. There were no complications, and after removal of the tracheotomy tube the wounds healed in two to seven days.

Thoracic conditions

Tracheotomy was used on 31 occasions in the following conditions: multiple fractures of the ribs, flaccid chest, crushed chest, open pneumothorax, subcutaneous emphysema, and gunshot wounds; also following cardiac or pulmonary surgery, and following cardiac arrest. Tracheotomy was performed at the first indication of paradoxical movement of the chest wall or of increased bronchial rales. The respiratory passages were kept clear by suction and most patients recovered without the pulmonary complications which would most likely have been fatal. In some instances of severe disability due to flail chest, we have found the apparatus of Kottke and Kubicek (5), as used by Jensen (6), to be of value. The tracheotomy tube is connected to an apparatus which delivers oxygen at a positive pressure. By this method, intrathoracic pressure during inspiration and expiration will always be above atmospheric pressure, and therefore paroxysmal respiration will be avoided.

Head injuries

Tracheotomy was used in 22 instances of head injury. Most of the patients were unconscious, unresponsive, and had rales in the bases of the lungs. Loud breathing was present, signifying adequate respirations. However, the presence of a duskiness bordering on cyanosis signified that though air readily entered the pharynx, larynx and upper trachea, alveolar respiration was not taking place because mucus was blocking the small bronchioles. Tracheotomy provided a route for suctioning a very profuse amount of thick tenacious sputum. Following this procedure the color of the patients improved markedly. Though the nature of the injuries prevented recovery of a fair number of the patients, the neurosurgical staff felt that tracheotomy was life-saving in most of the patients.

Abdominal postoperative conditions

After major abdominal surgery, it is common to have patients either refuse to cough or show a marked decrease in coughing efficiency. This is especially common in the older patient or in the short, fat individual.

Tracheotomy was instituted in 10 such patients in whom there was only a semblance of retained secretions. In almost all instances, immediate aspiration of large amounts of mucoid material was obtained.

Burns

Not infrequently, burned patients are admitted to the hospital who have inhaled smoke or hot fumes. Severe bronchitis results, and retained secretions complicate the picture. In 6 such cases we instituted tracheotomy, and beneficial results were obtained in all. In 1 instance the patient lived for ten days, during which time very viscous, tenacious mucus was constantly suctioned from his respiratory tract. Autopsy revealed the typical hemorrhagic bronchitis found in this type of injury. It was gratifying to note that his respiratory tract was entirely clear of accumulated mucus.

CONCLUSION

Tracheotomy results in both mechanical and physiologic benefit to the critically ill patient. The tracheo-bronchial tree can be easily and frequently aspirated by any member of the house or nursing staff. In addition, tracheotomy benefits by decreasing the volume of dead space in the respiratory tree and by diminishing resistance to inspiration and expiration.

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TWO UNUSUAL CASES OF PELVIC CANCER*

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Cancer obeys no set rules in its growth and spread, and its behavior is quite unpredictable. Dual or multiple primary cancers in the same individual, occurring either simultaneously or at different times, are not extremely rare (1, 2). Late recurrences or perhaps appearances of new cancers at the same site, occurring from five years to more than twenty years after apparent arrest of the orginal malignant lesion by irradiation or surgery, have always been of interest and indicate the need for re-examination of patients long after the five-year period of so-called "cure" (3).

Recently, 2 instances of pelvic cancer have come to our notice, which have followed so unusual a course as to be actually bizarre. In each instance, cancer of part of the uterus was arrested by irradiation therapy for more than ten years; then a second cancer of a different cell type appeared in another location in the same organ. The first instance was so impressively unusual that it was reported at one of our staff meetings (4). The patient in question registered at the Mayo Clinic in 1938, complaining of postcoital vaginal bleeding for the previous four months. Her age was 48 years. A diagnosis of carcinoma of the uterine cervix stage IV, was made; biopsy of the growth showed squamous-cell epithelioma, grade 3 (Fig. 1). A complete course of radium therapy with supplementary roentgen therapy was administered during June and July, 1938. Re-examinations over the next eleven years showed good healing and no evidence of recurrence.

Eleven and a half years after her treatments, that is, in January 1950, the patient returned because of recent slight vaginal bleeding. Vaginal smears showed malignant cells, the corpus uteri was enlarged, and curettage of the cervical canal revealed adenocarcinoma, grade 2. Limited radium therapy was started, but was discontinued because of the onset of hyperpyrexia and pyometra. After drainage of the uterus and a course of penicillin therapy, a radical hysterectomy and bilateral salpingo-oophorectomy was performed January 25, 1950. The pathologist found an adenocarcinoma, grade 3 (Fig. 2) of the upper part of the fundus of the uterus, penetrating the muscle to a depth of 1 cm. and extending over an area 7 cm. by 6 cm. The excised cervix showed no residual carcinoma. Six months later, in July 1950, vaginal-wall implants of adenocarcinoma, grade 3, were excised and the areas were treated with radium. In September 1952, a firm mass was noted in the left side of the pelvis and enlarged lymph nodes were present in the left groin. At the patient's last visit in February 1953, her general health had commenced to deteriorate; the pelvic mass had

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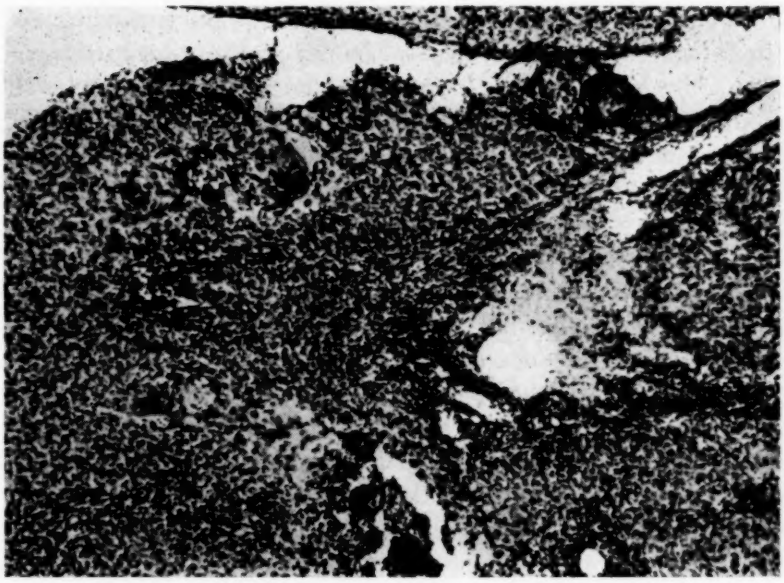

FIG. 1. Squamous-cell carcinoma of cervix (× 80).

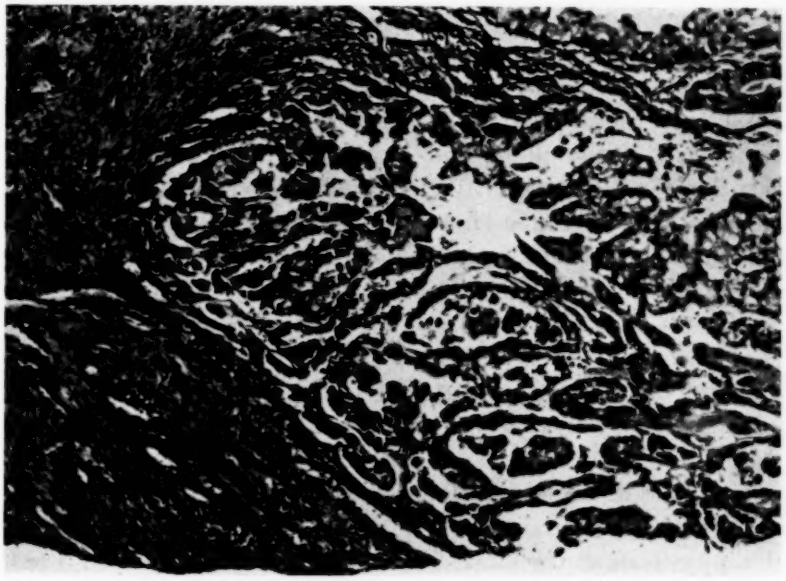

FIG. 2. Adenocarcinoma, grade 3, of the uterine corpus (× 80).

enlarged and broken through into the rectal lumen. Biopsies frnm the vaginal vault and from the rectum showed adenocarcinoma, grade 3. Because of the pressure of the growth on the bowel, a palliative colostomy was performed February 17, 1953. Certainly, up to the time of this visit, excellent palliation had been achieved in this case.

A similar instance was observed more recently. A patient, aged 55 years, registered at the clinic February 4, 1952, because of vaginal bleeding for the

preceding seven days and some abdominal pain for the preceding six months. Thirteen years before, in 1939, a cervical biopsy and uterine curettage had been performed in Chicago. There had been no evidence of malignancy in the uterine scrapings but the biopsy of the cervix had showed carcinoma. A slide had been mailed to us and our pathologist had diagnosed squamous-cell epithelioma, grade 3. The slide had then been returned. Radium therapy and roentgen treatment for carcinoma of the cervix had been given at Michael Reese Hospital in Chicago, in 1939. Frequent examinations in Chicago over the next six years showed perfect healing and no evidence of recurrence. Pelvic examination here in February 1952, revealed a normal cervix, but an enlarged uterine body. Scrapings from the uterus showed adenocarcinoma, grade 3. During February 1952, radium therapy was applied to the uterine fundus by the packing method, with additional treatments in the midcervix and vaginal cavity, plus roentgen treatment around the pelvis. Re-examinations here in June and September 1952, and February 1953, showed apparent arrest of the malignant lesion.

Since I became interested in this problem, a third case, not well authenticated, has come to notice. A patient registered at the clinic November 5, 1952; her age was 49 years and she gave a history of having had irradiation therapy elsewhere for carcinoma of the cervix ten years previously. Tissue from this cancer was not obtainable. A tumor over the right temporal area had appeared in July 1952, and a pinkish vaginal discharge began in October 1952. A radical hysterectomy was performed elsewhere for cancer of the uterine corpus, followed by postoperative roentgen therapy; slides of tissue removed at operation were studied by our pathologist at the clinic, and a diagnosis of carcinosarcoma was made. Examination here in November 1952, showed obvious recurrence at the vaginal vault. A biopsy from this area showed a mixed neoplasm, grade 4; there were also multiple metastatic lesions in both lungs and metastasis to the right temporal area. Limited palliative radiotherapy was carried out.

SUMMARY AND REMARKS

In 2 instances of cancer of the uterine cervix the patients were "cured" for more than ten years by irradiation therapy. Then carcinoma of a different cell type appeared in another portion of the same organ, this time in the uterine corpus. A third similar case is described, but not authenticated, since the original tissue could not be obtained.

In 1949, a physician at the Curie Foundation in Paris reported 3 cases of primary cancer of the uterus appearing after a cure by radiotherapy of another cancer of the same organ (5). The author speculated as to whether the second cancer, a growth entirely different from the original one, might have been caused by the heavy irradiation employed to cure the first cancer. He concluded that, although excessive radiation therapy may in rare instances be carcinogenic, usually eventuating in the appearance of a sarcoma, the presence of other unknown factors in tissue must operate along with the possible carcinogenic effect of irradiation, to produce another primary growth. This hypothesis is reasonable, since this type of case is so rare as to be almost unrecognized.

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AMERICAN THERAPEUTIC SOCIETY

THE 1954 ANNUAL MEETING

The 55th Annual Meeting of the American Therapeutic Society will be held at the Chase Hotel in St. Louis, Missouri, on *November 4, 5, 6 and 7, 1954*, just prior to the meeting of the Southern Medical Association. Members who wish to attend should write for reservations directly to the hotel, giving the time of arrival and departure.

The President, Dr. William B. Rawls, and the Program Committee are arranging an excellent program. Tentative plans call for symposia on lipid metabolism and on the newer drugs in the treatment of hypertension. Members who wish to submit papers for consideration by the Program Committee should send four copies of a title and a 200-word abstract to the Secretary, Dr. Oscar B. Hunter, Jr., 915-19th Street, N. W., Washington 6, D. C., by *August 1*. Two awards will be given this year to men who have made outstanding contributions to therapeutics.

The Chairman of the Local Committee on Arrangements is Dr. David B. Flavan, 401 Humboldt Building, St. Louis, Missouri.

PRELIMINARY PROGRAM

Thursday, November 4	
7:00 P.M.	Informal Get-Together Dinner
8:30 P.M.	Meeting of Council and Committee on Admissions
Friday, November 5	
	Registration
8:00 A.M.	Breakfast Meeting of Council and Committee on Admissions
9:00 A.M.	Business Meeting and Scientific Session
2:00 P.M.	Scientific Session
Saturday, November 6	
9:00 A.M.	Scientific Session
1:00 P.M.	Luncheon with the President
2:00 P.M.	Scientific Session - - - Business Meeting
7:30 P.M.	President's Reception
8:00 P.M.	Annual Banquet
Sunday, November 7	
12:30 P.M.	Brunch

THIRD INTERNATIONAL GERONTOLOGICAL CONGRESS—LONDON

The Third International Gerontological Congress will be held in London, England, *July 19–23, 1954*, under the presidency of Dr. J. H. Sheldon. Arrangements by the British Organizing Committee are well advanced. Dr. R. E. Tunbridge, B.M.A. House, Tavistock Square, London W.C.1, is Chairman of the Committee. An *American Committee* is cooperating with the British Committee, especially in regard to the program. Of this Committee *Dr. W. B. Kountz, 660 S. Kingshighway Blvd., St. Louis 10, Mo., is the Chairman.* The Congress will be both instructive and enjoyable. It is imperative for those planning to attend and to present their work, to send titles of papers, together with abstracts of not more than 250 words, to Dr. Kountz. As in the case of other International Congresses, personal invitations to present papers are not necessary but in the event that these would be helpful in obtaining subsidies for travel, the American Committee will be happy to request the British Organizing Committee to send official invitations.

The Research Committee on Biology and Medicine will meet at the same time as the Third International Gerontological Congress. The Chairman of this Committee is Dr. W. O. Thompson, Chicago, Illinois.

Because the time is short and it is difficult to get transatlantic reservations, except the more expensive ones, blocks of reservations are being held by Convoys Travel Service, 1133 Broadway, New York 10, N. Y. All correspondence concerning *travel information* should be addressed to *Mrs. V. Kelly, 660 S. Kingshighway, St. Louis 10, Mo.*

PROVISIONAL PROGRAM

July 19, A.M. Meeting of the Governing Body.
July 19, P.M. Official opening of Conference, followed by meetings of the Sectional Committees.
July 20, 21 and 22. Scientific Meetings of the Conference.
July 23. Closing Meetings of the Conference.

The meetings and discussions will be divided between three main sections of the Conference:

Section 1. Biology and Pathology.
Section 2. Geriatric Medicine and Psychiatry.
Section 3. Sociology and Psychology.

Discussions and symposia involving combined meetings of two or more sections, and meetings of the Research Group, are to be arranged.

Visits

Visits will be arranged during the meeting in London, to centers in and around London. After the Congress, tours will be arranged to other centers in the United Kingdom.

Opportunities will be given to members to see geriatric units in hospitals, residential homes, housing accommodations, clubs and special industrial facilities.

Proposed Provincial Tours

Following the main Congress, tours will be arranged to enable members to see something of the work for the elderly throughout the country. Local members have expressed the wish to meet members attending the Congress and to entertain them during the provincial visits.

The following tours are being arranged: 1). London, Oxford, then to the West Country, returning via Southampton and Salisbury to London. 2). London, Nottingham, Sheffield, Leeds, Harrogate, Durham, Sunderland, York, Lincoln and Cambridge, to London.

Social Occasions

July 19. President's Reception in the evening.
July 21. Evening Reception.
July 23. Conference Dinner.

Throughout the Congress, visits to centers of scenic and historic interest in and around London will be arranged. Opportunities will also be provided for members to meet informally.

RESEARCH COMMITTEE ON BIOLOGY AND MEDICINE OF THE INTERNATIONAL ASSOCIATION OF GERONTOLOGY

REPORT OF MEETING OF THE AMERICAN DIVISION, SAN FRANCISCO, AUGUST 25, 1953

A short meeting of the American section of the Research Committee on Biology and Medicine of the International Association of Gerontology was held during the meeting of the Gerontological Society, Incorporated, in San Francisco at the Marks Hopkins Hotel, Tuesday, August 25, 1953. The following members were present:

Dr. Warren Andrew
Dr. E. V. Cowdry
Dr. John Esben Kirk
Dr. Albert I. Lansing
Dr. N. W. Shock
Dr. W. O. Thompson, Chairman

These members of the Committee expressed interest in the ideas already set forth by Dr. V. Korenchevsky concerning the objectives of the Research Committee. Further consideration of the problem at the time of the meeting of the

International Congress in London, England, July 19–23, 1954, was considered desirable.

It was felt that elaborate plans for the meeting in London could not be made at the present time because no funds are available for traveling expenses of members of the Committee. In most instances, American investigators and clinicians who wish to attend the meeting in London must do so at their own expense.

W. O. THOMPSON, M.D.
Chairman, Research Committee on Biology and Medicine

A WORKSHOP ON AGING

Aging—Everybody's Business is the title of the University of Michigan's Seventh Annual Conference on Aging to be conducted as a workshop in Ann Arbor, Michigan, June 28–30, 1954.

The workshop will provide participants with the opportunity to exchange ideas with persons of varied experience, to define responsibility for the tasks that lie ahead, and to establish bench-marks for the creation of an environment in which the senior citizen can enjoy life-long development.

Leaders in health, business, employment, labor, education, rehabilitation, social work, religion, housing, recreation, community organization, city planning, and government are invited to attend, as are members and officials of fraternal organizations, women's clubs, service organizations, retirement groups, and voluntary organizations.

Older people are especially invited. They will have the opportunity to gain a better understanding of their role, and their participation will focus attention upon issues with which they are most concerned.

For further information, write to Dr. Wilma Donahue, Chairman, Division of Gerontology, 1510 Rackham Building, Ann Arbor, Michigan.

SCHERING AWARD FOR MEDICAL STUDENTS

SUBJECTS ANNOUNCED

To encourage scientific reporting and to stimulate medical students' interest in the ever expanding fields of therapy, the Schering Award Committee has announced the beginning of the ninth consecutive competition in 1954.

Titles of three subjects on which students in the United States and Canada are being invited to submit papers have been made known by George Babcock, Jr., M.D., chairman of the committee. They are:

1) The Use of Androgen Therapy in the Female
2) The Prophylactic and Therapeutic Uses of Parenteral Antihistamines
3) Modern Treatment of Infections and Allergic Disorders of the Eye

For the best paper on each of these subjects, the committee will present one $500 first prize and a $250 second prize. Special citations and professionally useful gifts will also be awarded to all students who submit papers of merit. Outstanding medical authorities in each field will judge the papers.

The deadline for entry forms specifying the student's chosen title is *July 1, 1954*. All manuscripts must be mailed not later than October 1. Students may compete individually or cooperatively in research teams.

The purpose of the Schering Award is to encourage original reporting, in the hope that students will later contribute to the essential communication of knowledge throughout the medical profession.

Information and instructions for the competition are available from Schering Corporation, 2 Broad Street, Bloomfield, N. J.